American Journal of Obstetrics and Gynecology

VOL. 55 MARCH, 1948 No. 3

Transactions of the Second Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, Ste. Marquerite, Quebec, October 27-29, 1946

EMBRYOLOGICAL DEVELOPMENT OF THE LEVATOR ANI MUSCLE*

R. M. H. POWER, M.D., M.S., F.A.C.S., MONTREAL, QUEBEC

BY WAY of preamble, it is relevant to dwell briefly on the anatomic arrangement and functional development of the vulval sphincteric musculature (Fig. 1). This muscular group derives its origin from the common cloacal sphincter to which the levator ani muscle is inextricably related. Both the cloacal sphincter and the levator ani are ultimately derived from the third and fourth sacral myotomes.

The morphological work of Eggeling (1896) and the embryological investigations of Popowsky (1899) have elucidated the relationships of the vulval sphincteric group. From the "primordial sphincter cloacae" there arises, both in the course of phylogeny and of embryology, a division into a sphincter ani externus and a urogenital sphincter. The sphincter ani may differentiate into several layers and become a trilaminar muscle. The urogenital sphincter also differentiates further, but in a more decisive manner. From it are developed the sphincter urethrae, the ischiocavernosus of either side, and a median bulbocavernosus retaining a tendineus raphe in the midline, and probably the transverse perinei, superficial and deep.

Difference of opinion exists regarding not only these latter muscles themselves but also the question as to where they belong, their isolation, and non-isolation. Among others, Henle and Gegenbaur recognized the existence of a single muscle placed around the membranous part of the urethra, while others

*Presented at the Second Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, Ste. Marguerite, Quebec, Oct. 27-29, 1946.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

described more or less independent muscles, attributing their names to different fibers, which was the practice in their times, e.g., Wilson, Guthrie, and Muller who described special periurethral fibers.

No less an authority than Luschka described the transverse perinei as a part of the levator ani muscle while others considered it a completely independent muscle. However, Gegenbaur, in his textbook, laid it down "that a morphological unity of all the muscles of the perineum exists, inasmuch as they develop from the primitive sphincter cloacae muscle." This was the guiding principle which stimulated Popowsky in his research.

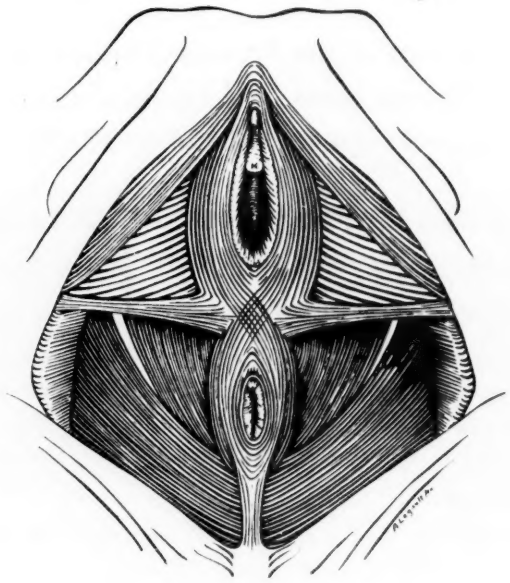


Fig. 1.—Schematic representation of the sphincteric muscular group of the pelvic floor. (Power, Surg., Gynec. & Obst., Sept., 1946.)

Popowsky, working with a series of young embryos, term babies, and adults, was able to demonstrate the origin of the sphincteric vulval group as arising from a single subcutaneous muscle, the sphincter cloacae (Fig. 2). I have repeated a large part of this work in the anatomic laboratory of McGill University, and my results, as far as they go, confirm Popowsky's conclusions.

In the early embryo the allantois and the hindgut terminate caudally in a common cavity, the cloaca. This structure, of course, corresponds to that found in the adult reptiles and birds, in which the orifice is surrounded by a sphincteric muscle. In the human embryo the allantois becomes separated from the cloaca by the ingrowth of a transverse mesodermal bar, thus forming the rectum behind and the urogenital sinus in front. The sphincteric muscle as a distinct entity can first be seen in a two-month human embryo. For the most part, this primitive muscle completely surrounds the orifices of the urogenital sinus and anus, but already a few fibers can be seen to decussate between these

two openings. The primitive cloacal sphincter is thus beginning to divide into a sphincter ani externus behind and a sphincter of the urogenital sinus in front.

With the sphincter ani externus we have no further concern. As already stated, it differentiates into a trilaminar muscle. Coming to the sphincter of the urogenital sinus, we may note that shortly after the sinus opens on the surface of the embryo, the ventral end of this muscle gains a slight attachment to the precartilaginous anlage of the os pubis. The ventral-caudal end of the urogenital sinus becomes differentiated into the urethra. Consequently, the ventral part of the urogenital sphincter develops into the sphincter of the urethra and migrates to a deeper plane. At a somewhat later date the conjoint caudal end of the Müllerian ducts which have made contact with the dorsal surface of the urogenital sinus push their way down along the posterior wall of the sinus to form the vagina; the dorsal end of the sphincter of the urogenital sinus surrounds the opening of the primitive vagina and differentiates into the sphincter vaginae or bulbocavernosus muscle. The sphincter of the urethra and the sphincter vaginae are still structurally continuous and are attached ventrally to the primitive pubis and from these the ischiocavernosus muscle develops.

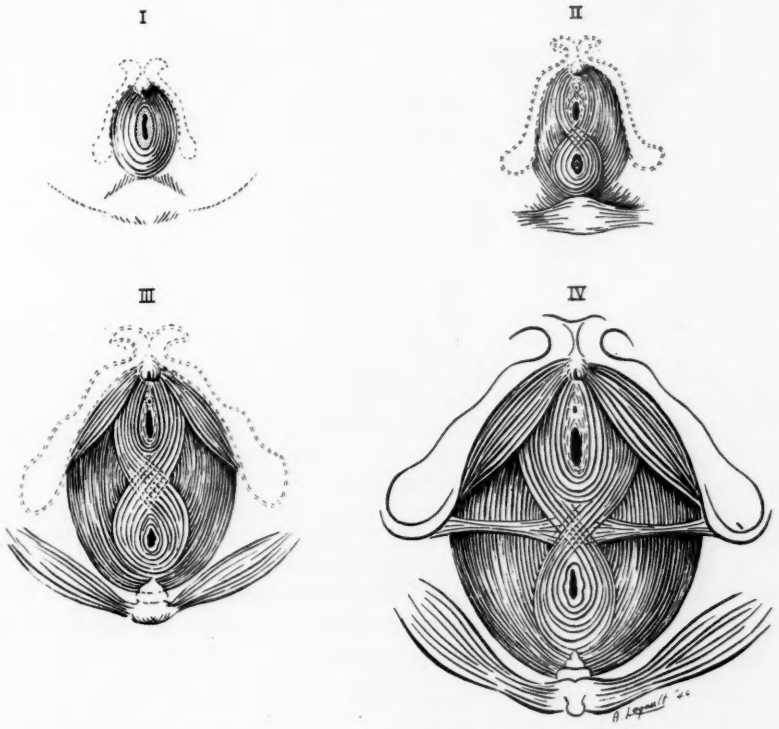


Fig. 2.—Successive differentiation of the cloacal sphincter in embryos of two, three, five, and seven months.

In the anthropoid apes the sphincter ani extends forward and forms a muscular diaphragm closing in the subpubic angle, and no true transverse perinei muscles are formed. In man this forward extension of the sphincter ani is not found, and instead we find that first a superficial and then a deep

transverse perinei muscle is formed. The deep transverse perinei is the last of the perineal muscles to appear in the human embryo and most of its development occurs postnatally. These two muscles apparently represent a development from the sphincter vaginae.

Practically nothing is known of the origin of the urogenital diaphragm. In some of the lower apes the fascia on the caudal aspect of the pubo-caudalis muscle forms a diaphragm in this region, but it is very doubtful if this is homologous with the human urogenital diaphragm. Wesson showed that in early life the human urogenital diaphragm is poorly developed and later acquires its characteristic density and strength. He regards it as a functional development, arising in man consequent to the upright posture and formed by a condensation of the fascia surrounding the muscles. The muscle mass in the embryo is covered on both aspects by a primitive connective tissue and in response to the functional requirements of the area, these sheets of connective tissue probably differentiate into the strong fascial lines of the urogenital diaphragm.

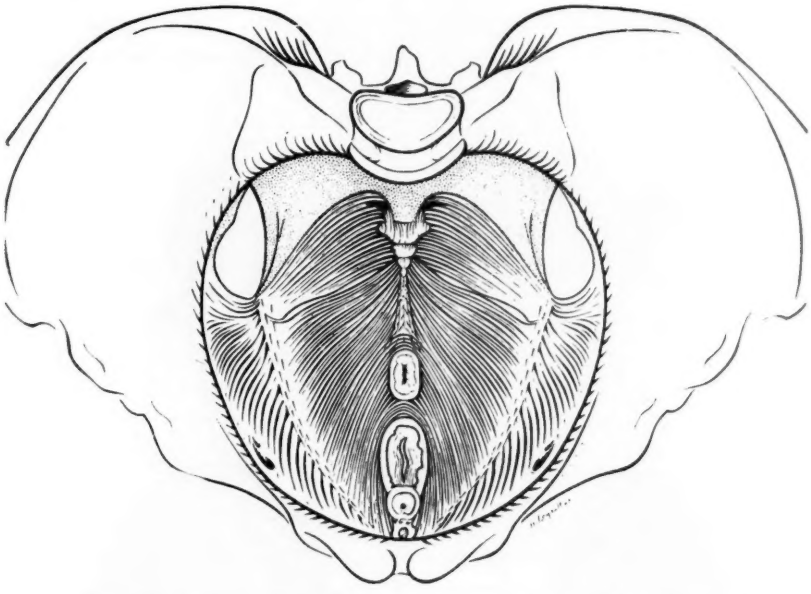


Fig. 3.—Levator ani muscle seen from above. Note anteriorly how pubococcygeal fibers are attached directly to the os pubis. Pubovaginalis and puborectalis fibers are clearly defined.

Davies describes the urogenital diaphragm as a continuity of the endopelvic fascia. This throws no light on its origin and is merely a statement that the various fascial layers in the pelvis are continuous with each other. This is a very usual phenomenon throughout the whole body.

In the lower monkeys the tail musculature is well developed and helps to support the viscera. It is composed of a strong pubocaudalis extending from the pubis to the tail and more laterally placed abductor caudalis muscles. The pubocaudalis passes beside the rectum but has no or only very slight attachments to it. In the anthropoids an anococcygeal raphe is present. The well-defined pubocaudalis finds some attachment to the rectum. The iliococcygeus and

coccygeus show tendinous changes. In man the pubocaudalis attains its maximum attachment to the rectum and forms a true puborectalis, while the iliococcygeus and coccygeus show further muscular and fascial regression. In its morphologic development the pubocaudalis experiences a regression in muscular elements with a compensatory development of tendon and fascia (Fig. 3).

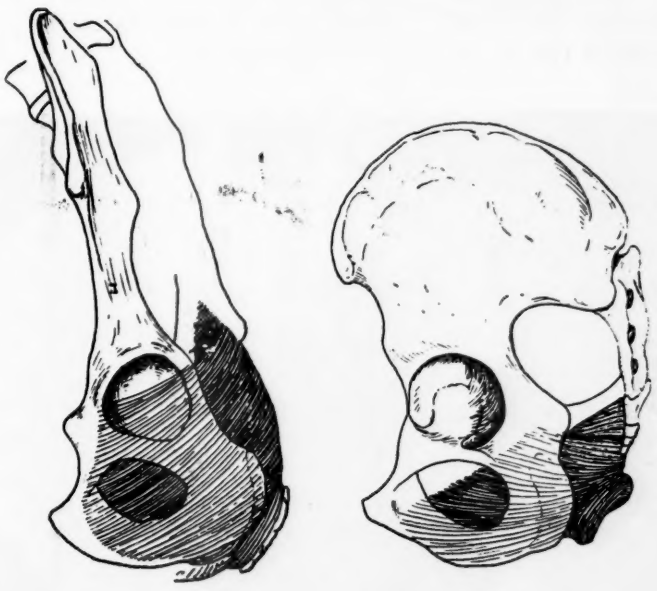


Fig. 4.—Lateral view of *(A)* great anthropoid, and *(B)* human pelvis. Note high cup-shaped arrangement of levator ani muscle in anthropoids with large external sphincter and cephalad termination of sacrum. In the human being the external sphincter is smaller and the triangular ligament is present, the sacrum is wider and terminates more caudally. Notice rotation of ilium in the human being.

To summarize, in the anthropoids the sacrum is situated very cephalad to the ischium; the pelvic outlet accordingly is a very elongated lozenge, the dorsal end being much cephalad to the ventral, and is weak, especially posteriorly. This is compensated for by an exceptional development of the sphincter ani externus which extends forwards as a muscular diaphragm into the urogenital area (Fig. 4). In man the bony pelvis is greatly shortened in a cephalic caudal direction and the wider sacrum terminates at a relatively lower level. The outlet, therefore, is very much shortened dorsoventrally, but is relatively broadened from side to side, especially in the anterior part. The pubocaudalis now is mainly attached to the rectum and anococcygeal body; the iliococcygeus has also moved its insertion on to the side wall of the anal canal and anococcygeal body, and the coccygeus muscle itself is more tendinous and forms the lesser sacrosciatic ligament. Compare, for example, a gorilla with a human pelvis (Fig. 5). Notice in the gorilla how cephalad the sacrum terminates; the complete absence of an ischial spine; the absence of a true sciatic notch, and the elongation of the whole pelvis as compared to the human being. In man the sphincter ani externus is much reduced and does not form a diaphragm, and in its place we find the deep and superficial transverse perinei muscles, and the urogenital diaphragm.

The skeletal musculature is derived almost entirely from the primitive segments. These may be said to begin with the segmentation of the dorsal divisions of the trunk mesoderm. The musculature arising from the primitive

segments is both phylogenetically and ontogenetically the oldest in the body. The development of many of the muscles in man and animals has never been traced and of the remainder our knowledge is fragmentary and incomplete.

The levator ani muscle is an evolutionary product representing the caudal flexor, abductor musculature of tailed mammals, which in man, as in anthropoid apes, with the reduction of the tail, has gained new relationships with the pelvic viscera. The coccygeus represents the proximal ventral caudal abductor of tailed mammals. No effort to verify the former statement in the human fetus is recorded in the literature to my knowledge.

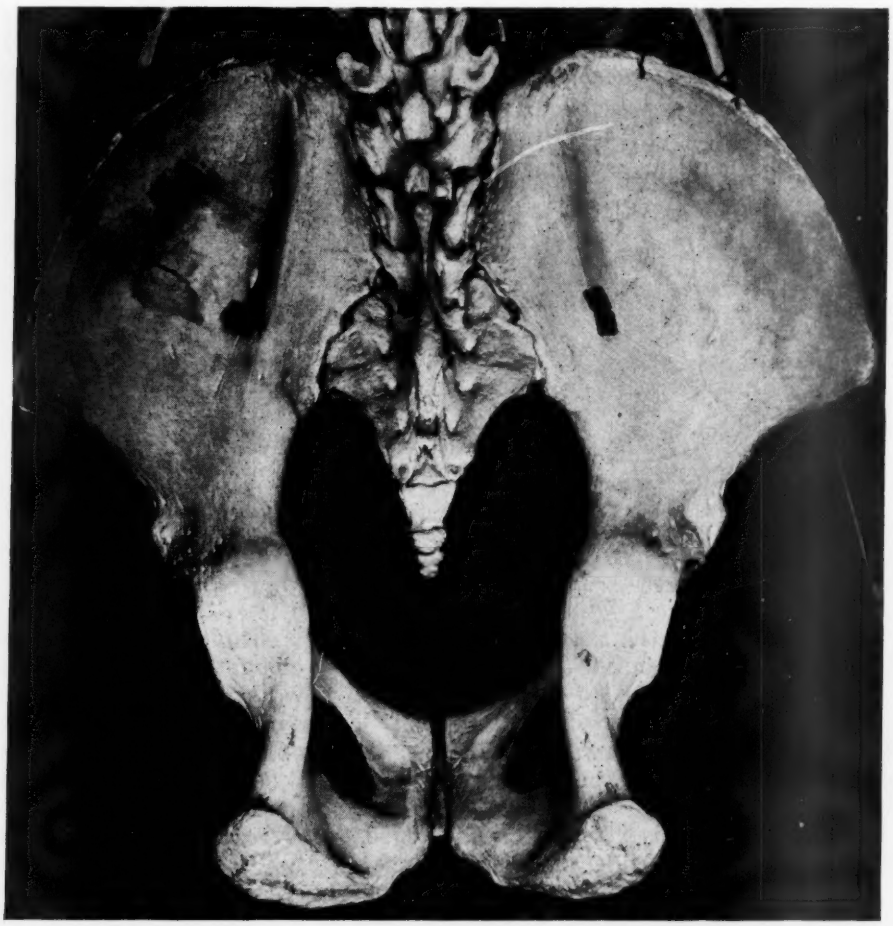


Fig. 5.—Gorilla's pelvis seen from behind.

Let us for a moment consider the recti group of the thoracoabdominal muscles which arise through the ventral extension of the thoracic myotomes into the body wall.

Certain fundamental processes are operative in the changes of the myotomes during the formation of adult muscles. Such processes may consist of a change in the direction or a migration of myotomes, fusion of portions of successive myotomes as in the formation of the rectus abdominis muscles, or a longitudinal or tangential splitting, or a degeneration of myotomes.

As the body wall develops, extensions of the myotomes migrate ventrally into these walls and the ventral ends of these extensions fuse together to form a ventral longitudinal muscle column from which the rectus abdominis and other elements are ultimately developed (Fig. 6).

Fig. 6.—Right side undifferentiated ventral longitudinal muscle column. Left side differentiated ventral longitudinal muscle column.

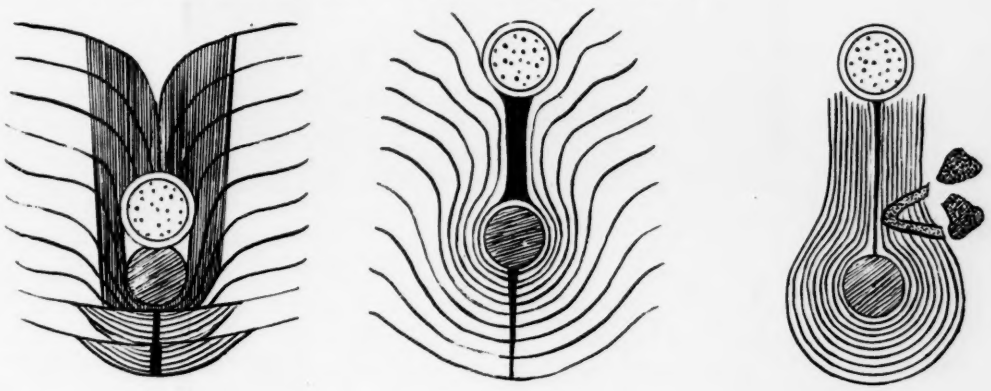


Fig. 7.—Diagrammatic representation of the formation of the lower end of the linea alba and the anovaginal cleft. A, The cloacal membrane extends onto the caudal surface of the umbilical cord. B, The cloacal membrane has migrated ventrally forming the upper end of the linea alba below the umbilicus. C, The cloacal membrane has reached the perineum. The pubic element growing in from the side cuts off the lower end of the linea alba to form the anovaginal cleft. (Dotted center represents the umbilical cord. Cross-hatched circle represents the cloacal membrane.)

The myotomes begin to grow into the body wall with the development and extension of the ribs. Even in a 7-mm. embryo, before the myotomes are fused into a continuous column, this process has already begun. In a 9-mm. embryo the myotome process extends further ventrally than do the ribs and ends ventrally in a continuous column on each side—the "rectus element" formed by the fusion of the entire myotome thickness.

This ventral longitudinal muscle column of each side ultimately forms the rectus abdominis and pyramidalis in the abdomen; the depressor muscles of the hyoid bone in the neck, while in thorax, owing to the development of the sternum, is not represented or is represented very occasionally by a vestigial sternalis muscle. At this early stage of the embryo we may note that the cloacal membrane is still on the caudal edge of the umbilical cord (Fig. 7). The primitive longitudinal ventral muscle column, therefore, extends between the two openings of the primitive alimentary canal; from the mouth to the primitive cloacal membrane. At a later stage the cloacal membrane migrates caudally into the perineum, and as it does it carries with it the original ventral cleft between the muscle column of either side. Thus are formed the lower part of the linea alba with the rectus abdominis muscles on either side.

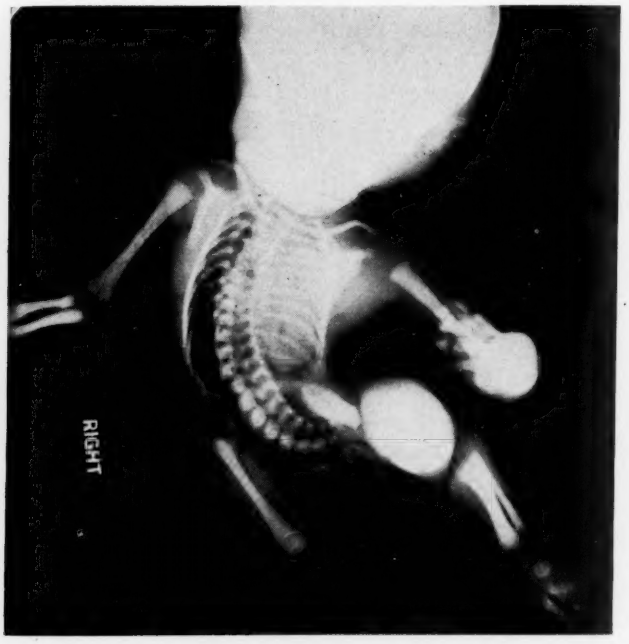
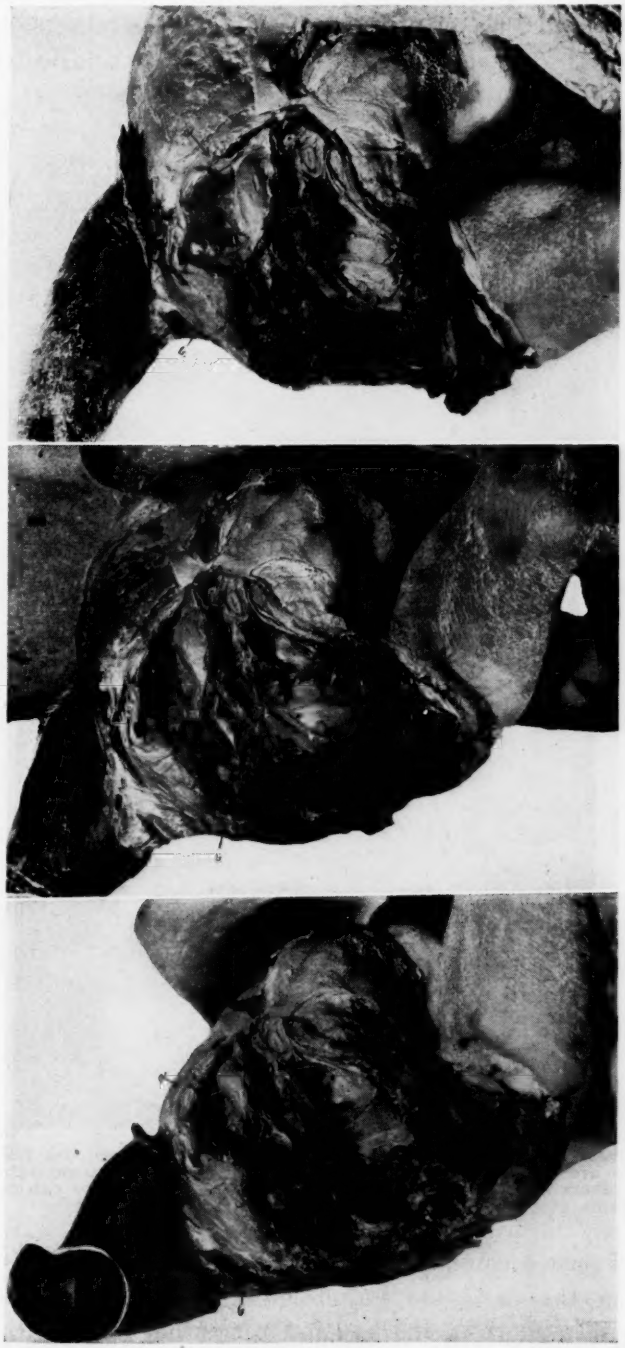


Fig. 8.—X-ray photograph. Note absence of pubic element on right side.

The levator ani muscle, as shown by its nerve supply, is undoubtedly derived from the fourth sacral myotome, and it is tempting to suggest that as this myotome migrates ventrally it becomes divided like the myotomes of the abdominal wall, into two portions; a lateral part, the iliococcygeus, forming a continuous sheath and corresponding roughly to the oblique muscles of the abdominal wall; and a ventral longitudinal column, the pubococcygeus, or pubocaudalis of lower forms, corresponding approximately to the rectus abdominis. If this view is substantially correct, the anovaginal cleft between the pubococcygeus of either side really corresponds to an extension of the linea alba, which was later cut off from the abdominal linea alba by the development of the

os pubis. The longitudinal muscle column of either side, therefore, still extends morphologically between the two openings of the alimentary tract, but is interrupted at two places—one, by the formation of the sternum, and two, by the formation of the os pubis. In other words, as the cloacal membrane migrates from the umbilical cord to the perineum it carries with it, so to speak, an extension of the linea alba, and also an extension of the tendency of the myotomes



A.

B.

C.

Fig. 9.—Dissection of eviscerated fetus. Diagrams *A*, *B*, and *C* with fetus tilted at varying degrees show continuity of rectus abdominis fibers terminating in right puborectalis muscle. *a*, Rectus abdominis fibers. *b*, Puborectalis fibers.

to form a longitudinal muscle column on each side of the linea. This view of the structure of the levator ani muscle, which I owe to Professor C. P. Martin, means that the structure of this muscle presents many analogies with that of the anterior abdominal wall muscles.

Again, if this view is substantially correct we might expect that, in cases where the os pubis is absent, or imperfectly developed, the lower end of the rectus abdominis and the ventral end of the puborectalis ought to be structurally continuous. Through the kindness of the Pathological Department of McGill University, I was permitted to dissect a case of ectopiae vesicae in which the pubis was totally absent on the right side and was only represented by a small element on the left (Fig. 8). Figure 9 is a dissection of the right side of the abdominal wall and perineum. It shows the rectus abdominis passing without a break into the puborectalis. This terminates to the left of the coccyx. On the left side rectus abdominis fibers passed directly to the pubic element, while about halfway between the umbilicus and this element other

Fig. 10.—Transverse section, seven-week fetus, just beneath the pubic element. Some cartilaginous cells are present. On the left side note differentiation of pubococcygeal (*a*) and iliococcygeal (*b*) fibers to the anterior face of the pubis. These fibers run obliquely caudalward in an anteroposterior direction.

fibers split and passed caudally in juxtaposition to and behind the large bowel, disappearing in the perineum posterolaterally to the displaced anus. The perineum was very short on the left and it was not possible to dissect the left puborectalis.

Efforts have been made to follow the development of these muscles in detail in the human embryo and are still under way. We are not yet in a position to make a positive statement as regards the human embryo, but we have many indications that lend support to our view (Figs. 10, 11, and 12).

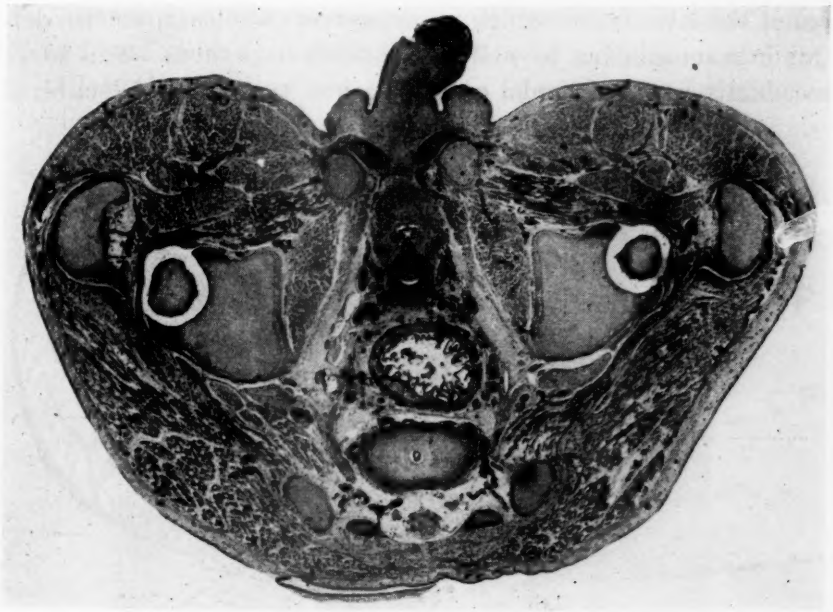


Fig. 11.—Two-and-one-half month fetus. Transverse section through acetabular region. Notice obturator internus muscle medial to which are the pubococcygeal fibers, extending anteroposteriorly.

Fig. 12.—Actual dissection of four-month fetus showing pubococcygeal and puborectalis fibers. In a younger fetus the caudal end of the vertebral column is almost vertically beneath the pubic element. Thus the puborectalis and rectus abdominis fibers are almost in a straight line.

In support of this view we may note that in the selacians, the pelvic floor is formed by a backward continuation of the rectus abdominis. (Kieth and Paramore, *Lancet,* May, 1910.) The pelvic part of the rectus is attached behind to the tail; anteriorly it is attached to the movable pelvic girdle. The cloaca of the dogfish passes out between the right and the left primitive representatives of the levator ani, which can compress the cloaca, not by depressing the tail, as in mammals, but by pulling the pelvis backwards. This would make the pubocaudalis simply a caudal continuation of the rectus abdominis element.

Fig. 13.—Drawing of adult dogfish, ventral surface. M = Myotomes. T = Transverse pelvic bar. C.P. = Caudopelvic strand.

A pelvic floor can scarcely be said to exist in the fish, for the pelvis is rudimentary. In the dogfish (Fig. 13) the pelvic girdle is represented merely by a transverse bar of cartilage placed in front of the cloaca. It is unconnected with the vertebral column except by means of that part of the lateral trunk musculature which extends forwards from the tail into the body and which, as it passes over the pelvic bar, sends a good strand of its lowermost fibers to be inserted into its upper and lateral part. This strand of fibers, which forms part of the central tail musculature, from which it cannot be differentiated, is directed from behind forwards to the pelvic bar and may be called the caudopelvic strand.

In amphibians the recti and puborectalis are in the same straight line, interrupted by the os pubis (Figs. 14, 15, and 16). The recti abdominis and external obliques are attached to the pelvis; their contractions can become efficient only by fixation of this structure. This fixation was primarily attained by the development of the caudopelvic muscles, which thus anchored the pelvis posteriorly. The caudopelvic muscles are relatively of considerable strength, and pass caudally from the pelvis almost in the same straight line as the recti abdominis, and thus are admirably adapted to resist a displacement of the pelvis forwards which contraction of the recti tends to bring about.

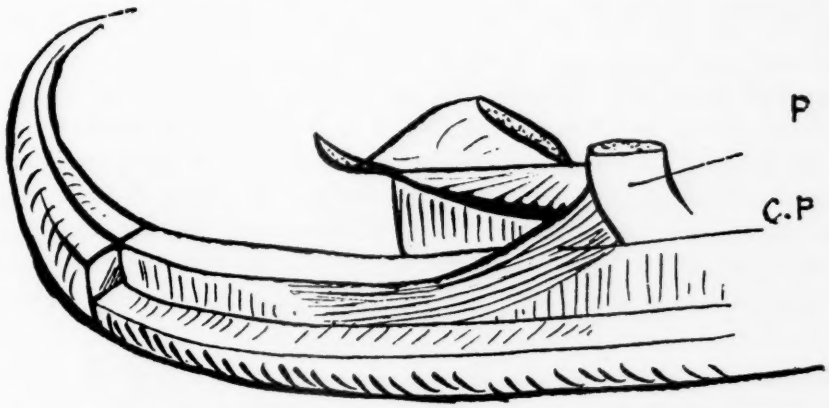


Fig. 14.—Dissection of cloacal region of the dogfish. About one-half life size. *P* = Pelvic bar bisected and turned outward. *C.P.* = Caudopelvic strand.

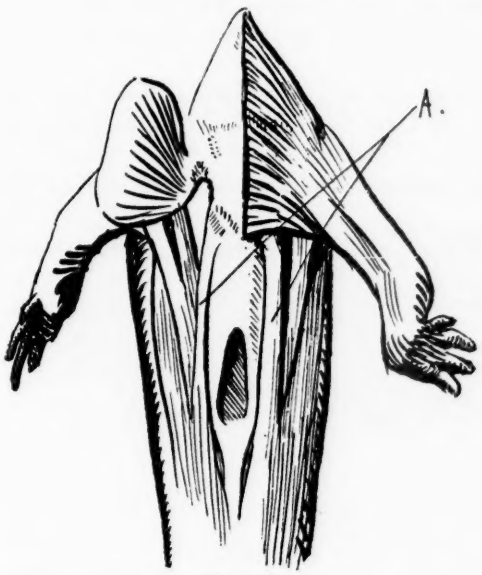


Fig. 15.

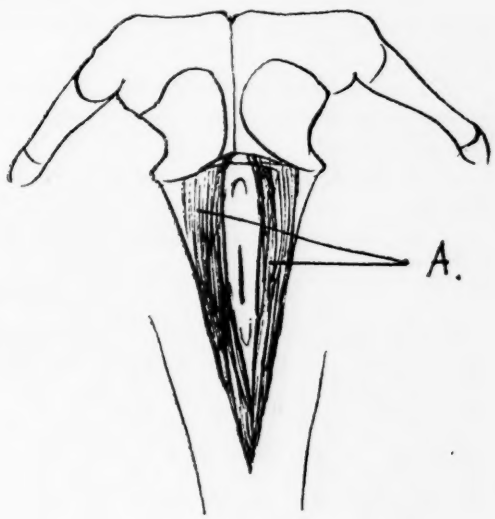


Fig. 16.

Fig. 15.—Dissection of menobranchus showing caudopelvic muscles. *A*, The cloacal passage has been cut through on a plane with these muscles, and the superficial parts have been removed.

Fig. 16.—Dissection of salamander maculosus to show *A*, caudopelvic muscles. (After Paramore.)

Lastly, this way of looking at things may possibly help to explain such abnormalities as ectopiae vesicae and epispadias, for, if the cloacal membrane, in its caudal migration, developed abdominal adhesions in the region of the umbilicus it could well happen that a stretched and attenuated ventral wall to the allantois would be left in the linea alba and would subsequently rupture, forming an ectopiae vesicae. Moreover, when the genital tubercle began to form near the caudal end of the cleft, we can easily see that its ventral and cephalic surface might include the caudal end of this attenuated membrane. In the perineum, however, the deficiency in the membrane is most likely made good by development of the sphincteric group of muscles and the urogenital diaphragm.

Finally, we may note that the width of the true pelvis is only about one third of that of the abdomen. Consequently, the viscera in the pelvis fill up most of the pelvic floor and separate the peritoneum from the pelvic diaphragm. The viscera really are lying embedded in a mass of connective tissue which forms the various layers of the endopelvic fascia. It is therefore easy to see why hernias through the pelvic floor are rare. The pelvic diaphragm is not a thin muscular layer in contact on its deep aspect with the peritoneum like the anterior abdominal wall. The vagina, in fact, forms the one weak spot in the pelvic floor and it is here alone that we find hernias as cystocele, rectocele and prolapse.

Material used in the preparation of this paper included numerous fetuses from five weeks to term, supplied to me by various members of the Obstetrical and Gynecological staffs of The Royal Victoria Montreal Maternity Hospital, the Jewish General, the Misericorde, and St. Mary's.

Dr. George Corner, Director of Embryology, Carnegie Institute, Baltimore, Maryland, made available to me two sets of stained serial sections of the fetal pelvis, 89 and 112.5 mm. C.R.L.

I am indebted to Professor C. P. Martin for his courtesy in permitting free use of the collection of specimens in Primate Anatomy and also for the great personal assistance he has afforded me.

Dr. S. M. Friedman, Assistant Professor of Anatomy, made several excellent diagrams for me.

May I express my gratitude to those who so kindly placed this material at my disposal.

References

1. Adair, F. L.: Am. J. Obst. **78**: 175-199, 1918.
2. Arey, L. B.: Contrib. Embryol. No. 168, 1938.
3. Bardeen, C. R., and Lewis, W. H.: Am. J. Anat. **1**: 1-35, 1901-02.
4. Barrett, C. W.: West. J. Surg. 146-152, 354-360, 1945.
4a. Davies, G. W.: Surg., Gynec. & Obst. **54**: 495, 1932.
5. Derry, D. E.: J. Anat. & Physiol. **42**: 97-106, 1907.
6. Elftman, H. O.: Am. J. Anat. **51**: 307-346, 1932.
7. Eggeling, H.: Morph. Jahrb. Bd. **24**: 405-511-768, 1896.
8. Falk, E.: Verh. Berl. med. Ges., Bd. 30, S. 290, 1899.
9. Franz, K.: Beitrag zur Geburtsh. u. Gynakol. Bd. 13, S. 12, 1908.
10. Gegenbaur, C.: Lehrbuch der Anatomie des Menschen. 603-610, Leipzig, Engelmann, 1883.
11. Henle, J.: Handbuch der Eingeweidelehre des Menschen, 462-469, 535-546. Braunschweig, Vieweg & Sohn, 1873.
12. Hill, H., and van Del, D. T.: Surg., Gynec. & Obst. **54**: 108-116, 1932.
13. Jones, F. W.: J. Anat. & Physiol. **46**: 228-238, 1912.
14. Kennedy, J. W., and Campbell, A. D.: Vaginal Hysterectomy, Tb. 402-428, 1942.

15. Kollmann, J.: Handatlas der Entwicklungsgeschichte des Menschen. Erster Teil. Fg. 292-295, Jena, Fischer, 1907.
16. Low, J. W.: Proc. Zool. Soc., Lond., Vol. I, 245, 1929.
16a. Luschka, H.: Anatomie des Menschen, Tubingen, 1863.
17. Mall, F. P.: J. Morphology. **14**: 1898, Am J. Anat. V. 433, 1905-06.
18. Meyer, A. W.: Calif. & West. Med. **27**: 769-774, 1927.
19. Martin, C. P.: McGill University, Personal communication.
20. Patten, B. M.: Human Embryol., 297-314-505-607, 1946.
21. Petersen, H.: Arch. f. Anat. u. Entwickl., p. 67, 1893.
22. Popowsky, J.: Anatomische Hefte. **12**: 15-48, 1899.
23. Pryor, J. W.: Anat. Rec. **25**: 257, 1923.
24. Poirier, P., and Charpy, A.: Anatomie Humaine, Vol. V. 1, 618-693, Paris, Masson, 1907.
25. Power, R. M. H.: Am. J. Obst. & Gynec. **38**: 27-39, 1939; Surg., Gynec. & Obst. **79**: 390-396, 1944; Surg., Gynec. & Obst. **83**: 296-311, 1946.
26. Steele, K. B., and Javert, C. T.: Am. J. Obst. & Gynec. **43**: 600, 1942.
27. Thomson, A.: J. Anat. & Physiol. **33**: 359-380, 1898-9.
28. Thomson, P.: The Myology of the Pelvic Floor, McCorquodale, London, 1899.
29. Todd, T. W.: Am. J. Anat. **31**: 345, 1923.
30. Trench, E. M.: Am. J. Anat. **59**: 333-345, 1936.
31. Waldeyer, W.: Das Becken, 123-128 & 192-211, Bonn, Verlag Cohen, 1899.
32. Wesson, M. B.: Calif. State J. Med. **20**: 269-272, 1922; J. Urol. S., 339-359, 1922; J. A. M. A. **81**: 2024-2030, 1923.

PLASMA PROTEINS IN PREGNANCY*

J. L. MACARTHUR, M.D., MONTREAL, QUEBEC

PROTEIN metabolism has been under investigation for nearly one hundred years, but it is only recently that hypoproteinemia has been recognized clinically. The present study was undertaken to determine if a simple method of estimating plasma proteins could be adapted to routine use in office obstetrics, while being sufficiently accurate to be clinically useful. Its application to a group of patients is described and discussed.

A short reference to the physiological and clinical aspects of the plasma proteins will first be made. Much of the evidence in the literature is of a conflicting nature, but certain assumptions appear to be reasonable.

Structure and Function of Plasma Proteins

The plasma proteins include albumin, globulins, and fibrinogen. The albumin fraction is clinically the most important protein in the plasma, maintaining osmotic pressure and viscosity. The globulins take part in antibody formation, and fibrinogen in blood clotting. It is unusual for either to be appreciably lowered in hypoproteinemia, which is always due to a depression of the albumin fraction.[1, 3-14]

The plasma proteins are maintained either by an adequate intake of protein or when this is lacking, by the so-called reserve stores. These stores cannot be distinguished from the rest of body protein, but participate in the continuing metabolism of the individual. That they are located in the vital organs principally is suggested by the finding that during protein starvation, the liver, kidney, and alimentary tract rapidly give up 30 per cent to 40 per cent of their protein, while that within the muscle remains unchanged.[16] However, as starvation proceeds, plasma[15] and muscle proteins are called on to maintain these organs above their vital levels, and a decrease in the concentration of plasma proteins occurs.

Source of Plasma Proteins.—The plasma proteins are synthesized within the body, from amino acids. The liver is the primary site of formation, but a secondary source, within the reticulo-endothelial system, is suggested to explain the occurrence of nutritional edema, in the presence of a normally functioning liver, adequate intake of protein, and positive nitrogen balance.[17-22]

Causes of Hypoproteinemia.—Protein deficiency in the tissues is recognized, almost solely, by a decrease of protein in the blood, with a resulting loss of osmotic pressure. When the albumin fraction falls below 3 Gm. per 100 c.c. edema occurs.[1] Hypoproteinemia may be due to[2]:

1. *Excessive loss of plasma:* In addition to the plasma loss due to hemorrhage or burns, excessive exudation into the peritoneal cavity, or intestinal walls, occurs in peritonitis, ascites and acute obstruction.

2. *Faulty nutrition:* A lack of sufficient quantity or quality of protein in the diet, or improper absorption of an adequate intake results in hypoproteinemia.

*Presented at the Second Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, Oct. 27-29, 1946.

3. *Excessive loss of nitrogen:* Operations, various forms of trauma and general anesthesia, cause excessive destruction of protein, and a large amount of nitrogen is lost in the urine. In hyperthyroidism the loss is due to the increase of metabolism.

4. *Defect in synthesis:* Due to its important role in the production of albumin, liver insufficiency is accompanied by severe hypoproteinemia. The defect is not due to faulty nutrition because positive nitrogen balance can be maintained.

Replacement of Plasma Proteins

An adequate intake of biologically valuable protein will prevent hypoproteinemia.[23, 26] If acute depletion has occurred, diet, intravenous amino acids, protein hydrolysates, or plasma will bring about restoration of normal plasma protein levels if used in sufficient quantities to maintain nitrogen equilibrium.[24] When depletion has been of long duration, plasma protein replacement, even with very high intake, may take months.[25] In cases of nephrotic and hepatic hypoalbuminemia, the restoration of normal plasma protein levels is notably ineffective.

Until recently, the diet of pregnant women was restricted in its protein content because it was thought to be toxic for the prospective mother. The observation that the patients who ate meat, eggs, and fish seemed to do better led to a study of plasma protein levels.[27] Hypoproteinemia was commonly found in pregnancy, and became extreme in toxic patients. It is now generally accepted that high protein intake in pregnancy will appreciably decrease the incidence of toxemia.[28]

Simplified Method of Estimating Plasma Protein

Measurement of plasma protein concentration by Kjeldahl analysis is a highly technical procedure, and requires elaborate and expensive apparatus. For these reasons it is beyond the reach of the clinician. The use of gravity methods have failed to be satisfactory, until recently, because the organic liquids employed were highly volatile and explosive.[29] These difficulties have been overcome by the use of an aqueous solution of copper sulfate, which has a coefficient of thermal expansion almost identical with blood or plasma, and rapid protein coagulating power.

Compared with plasma protein determination by Kjeldahl analysis, the copper sulfate method has proved to be accurate to within ±0.3 Gm. per 100 c.c.[29, 30, 31] The stability of the solutions, the rapidity and simplicity of the test, make it ideal as an office procedure.

Blood is withdrawn from the superficial vein of the arm, and allowed to fall into solutions of copper sulfate of known specific gravity. Its behavior after the loss of initial momentum depends entirely upon its specific gravity as compared with the solution into which it has fallen. The ideal anticoagulant for this test has been shown to be heparin.

Application of Test.—The present study has been carried out on a total of 600 normal patients, and a small number with toxemia. The greatest number, totalling 450, were patients attending the prenatal clinic of the Catherine Booth Hospital, but a smaller number were studied in practice on the private maternity ward of the Montreal General Hospital.

Fig. 1 shows the average levels on the group of normal clinic patients. There is a steady fall throughout pregnancy with a rapid rise post partum; although clinically normal, these patients seem to show hypoproteinemia. An almost identical result was obtained with the private patients, even though one would expect a much higher level in this group whose income would allow a more expensive high protein diet (Fig. 2).

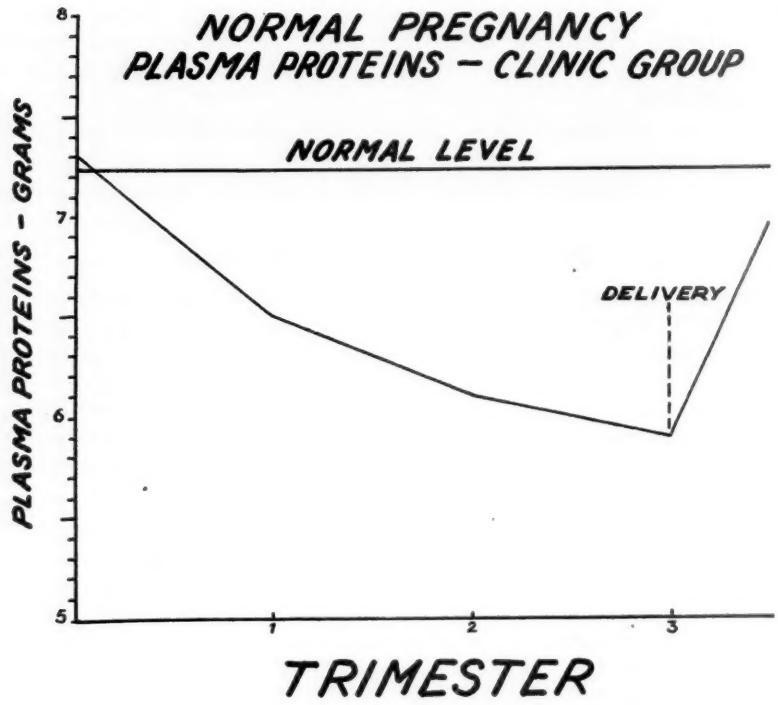

NORMAL PREGNANCY
PLASMA PROTEINS – CLINIC GROUP
NORMAL LEVEL
DELIVERY
PLASMA PROTEINS - GRAMS
8
7
6
5
1
2
3
TRIMESTER

Fig. 1.

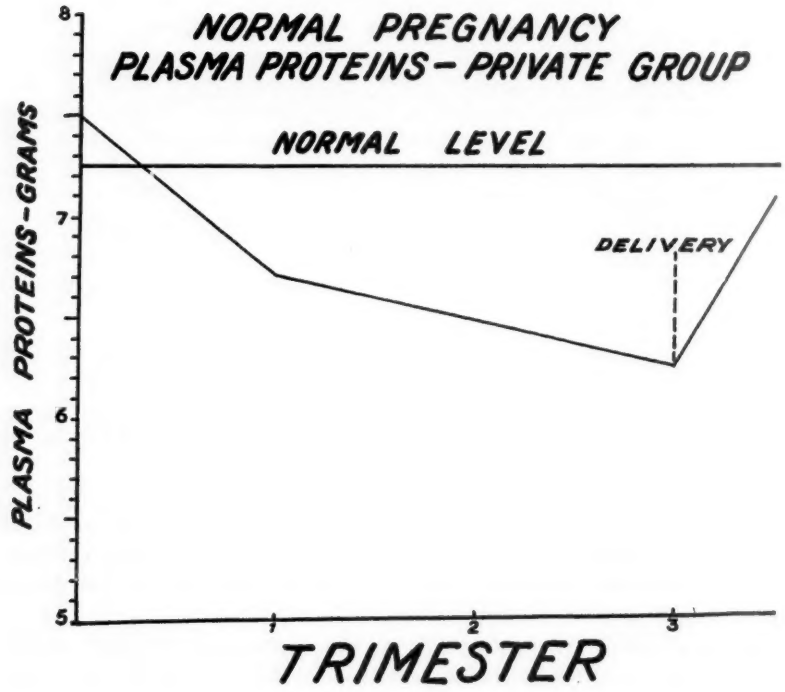

NORMAL PREGNANCY
PLASMA PROTEINS – PRIVATE GROUP
NORMAL LEVEL
DELIVERY
PLASMA PROTEINS-GRAMS
8
7
6
5
1
2
3
TRIMESTER

Fig. 2.

The similarity might be explained by the increased hydration of the blood during pregnancy. Hematocrit estimations will reflect changes in blood volume, and can be determined from the specific gravities of blood and plasma.[32, 33]

When estimated in this manner, they were found to be consistently lower than those obtained by centrifuge, and more accurate as a measurement of the true cell volume within the circulation.[34]

Protein and hematocrit levels expressed in terms of percentage are practically identical throughout pregnancy (Fig. 3). The hypoproteinemia coincides with the increased plasma volume, and to estimate the true level of plasma proteins the percentage of dilution should be added. Fig. 4, which represents such correction applied to our series of normal patients, shows the plasma proteins well within the normal range.

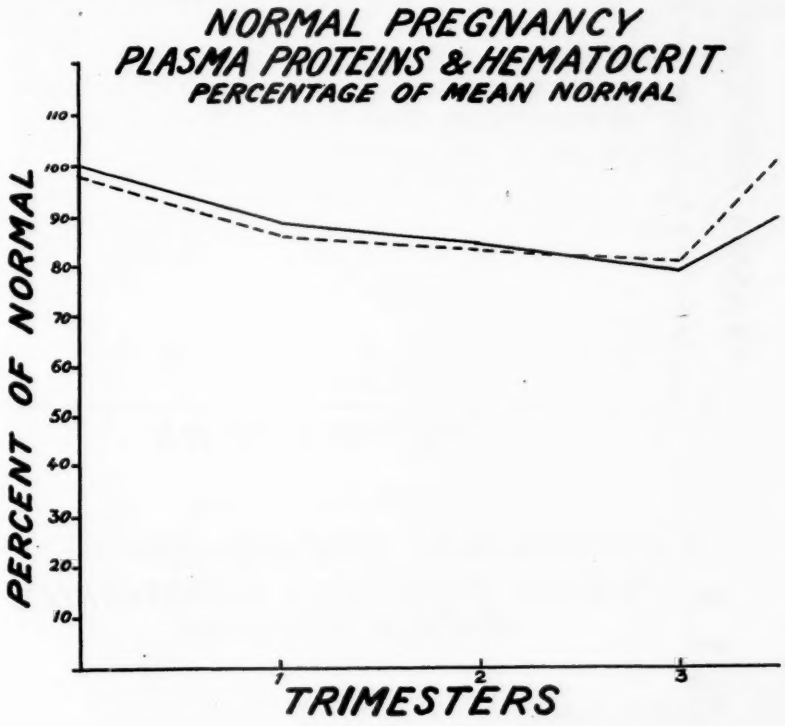


Fig. 3.

After correction for plasma dilution, such normal levels have not been present in the patients with toxemia. Figs. 5 and 6 show a marked difference between the hematocrit and plasma protein levels. In pre-eclampsia, a difference of 30 per cent was found, while in eclampsia the difference became more marked, as the hematocrit levels rose, and the plasma proteins fell. The relationship between hematocrit and protein levels may prove to be a valuable diagnostic aid in toxemias—an increase in difference between them is a poor prognostic sign, while a decrease in difference suggests improvement.

Protein Hydrolysates

During the course of this study, an attempt was made to evaluate the effects of supplementary feedings with protein hydrolysates by mouth and vein, in the normal patients and those with toxemia.

For this purpose, a group of twelve patients attending clinic were fed hydrolyzed protein over a period of three weeks, in the form of an enzymatic digest of casein. A daily supply of 100 Gm. of protein in this form was given

each patient. Plasma protein determinations were made at biweekly intervals. Over the three week period, no elevation of the plasma proteins occurred (Fig. 7).

The use of hydrolyzed protein in toxemia has been, of necessity, limited, through the lack of time imposed by the precarious condition of such patients,

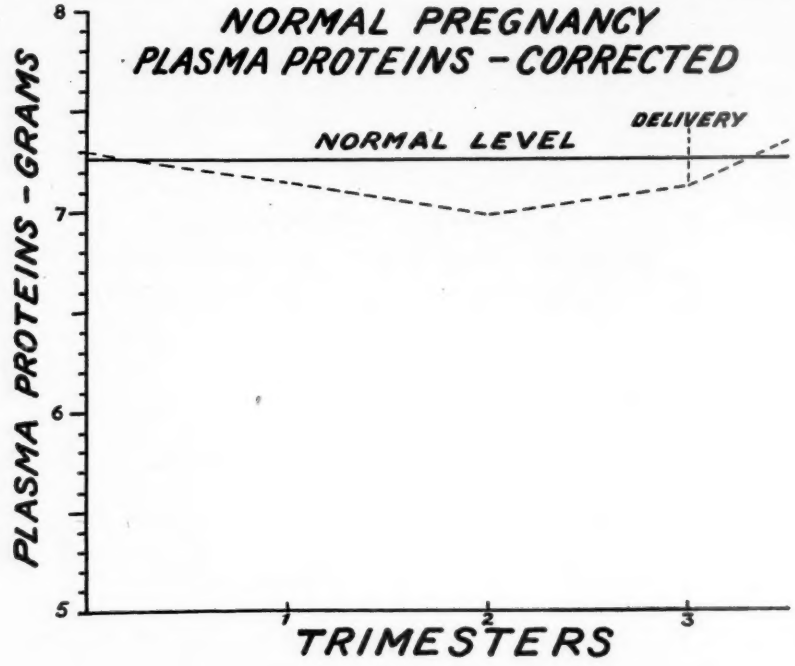


Fig. 4.

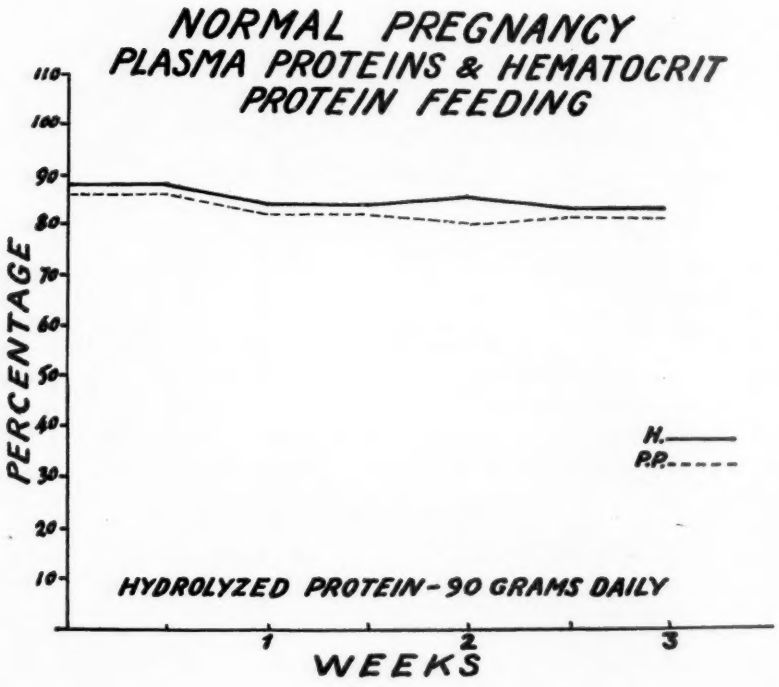


Fig. 5.

who usually must have their pregnancy terminated soon after admission to the hospital. In our experience, the plasma proteins rise rapidly post partum in both the normal and toxic patient, and they have not been included.

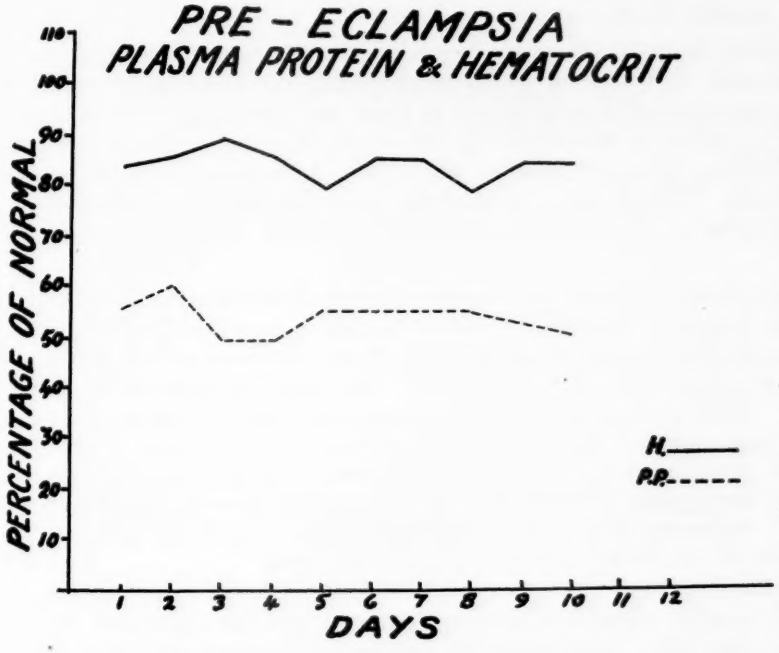


Fig. 6.

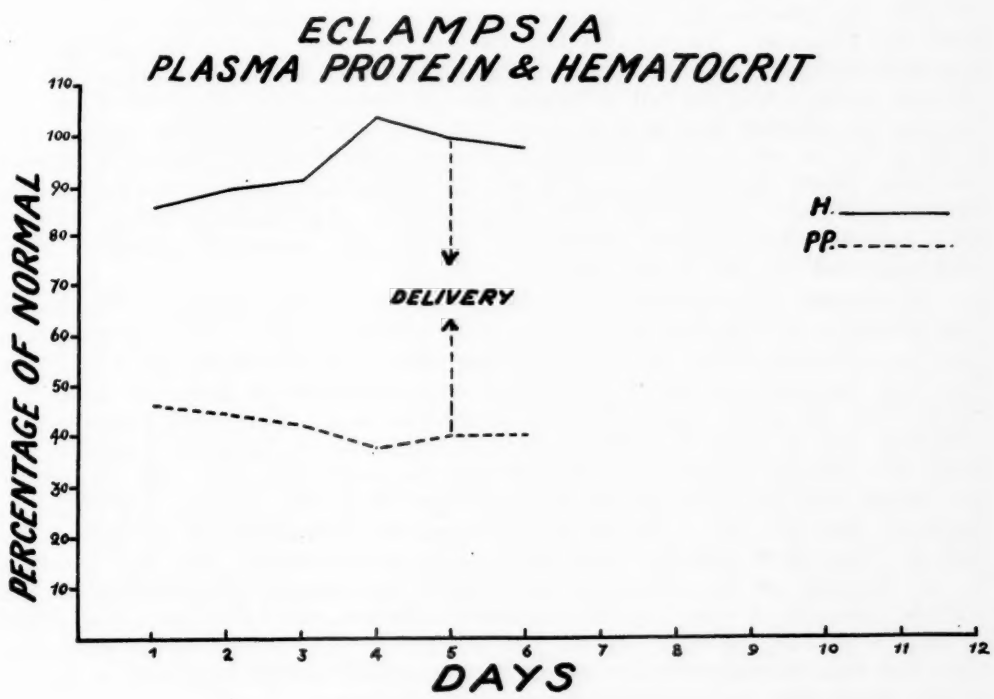


Fig. 7.

The response to oral hydrolysate supplements prenatally was observed in three cases of pre-eclampsia. In two of them, a daily supplement of 100 Gm. was given over a period of six days, while the third patient was given 200 Gm. daily for four days. No improvement was noted in edema, albuminuria, or plasma protein levels.

Similar observations were recorded when protein hydrolysates were given intravenously. With the preparation used, reactions were common, and included severe vomiting, abdominal pain, and flushing. They appeared when the rate of infusion exceeded 7½ Gm. an hour, or when the preparation was not well diluted. Adequate dosage was difficult because it was necessary to limit fluid intake. Strict routine toxemic care was given simultaneously, so that interpretation of the results was difficult. The record of two patients is included.

One patient entered the hospital with a diagnosis of toxemia of pregnancy. She had gained 12 pounds in weight during a two-week period, with associated edema, and increase in blood pressure from a usual level of 120/70 to 150/100. The urine remained free of albumin. Her plasma proteins on admission were 3.9 Gm. Therapy included bed rest, sedation, a high protein, salt-poor diet, and intravenous protein hydrolysate, totalling 30 Gm. daily. No improvement resulted. Over a period of five days, plasma protein concentration decreased to 3.7 Gm., her weight increased 5 pounds, edema became more noticeable, blood pressure remained unchanged, and her urine output diminished. Premature separation of the placenta and still birth occurred.

Another patient was admitted with eclampsia. Convulsions were frequent, and only partial consciousness was regained between seizures. Her blood pressure was 160/110, almost complete anuria was present, and the albumin content was 10 Gm. per liter. Manifestly, no one should jeopardize the life of such a patient by relying on a measure not proved by clinical trial. Accordingly, morphia and magnesium sulfate were given, and Stroganoff's method of treatment was followed. An intravenous injection of glucose and hydrolyzed protein was administered. Convulsions ceased shortly after treatment was started, and did not recur. A rapid fall in blood pressure, increase in output of urine, and decrease in albumin were noted. Over the next four days, a daily intravenous of 60 to 90 Gm. of protein was given. Reactions were marked but not alarming. The fetal heart sounds disappeared on the second day, and on the fourth day spontaneous labor terminated with the expulsion of a stillborn baby, followed by a prematurely separated placenta. The plasma proteins on admission were 3.98 Gm., and 3.7 Gm. at the time of delivery.

Methionine.—Methionine was administered to a single patient in this study. The patient was admitted to hospital with pre-eclampsia. She had first been seen in February, 1946, and her expected date of confinement was October 3. She was examined at monthly intervals and, previous to Aug. 22, 1946, her weight had increased from 150 to 174 pounds only. Her blood pressure had remained low, around 110/160, and there had been no albumin found in the urine. On this day, Aug. 22, 1946, however, she was found to be very edematous, her weight had increased in one month from 174 to 195 pounds, and the blood pressure was 185/110. The urine contained an abundance of albumin. She had no complaints, and the fetal heart tones were normal. She was admitted to the hospital on the following day, where her weight was recorded at 196 pounds, albumin 4 Gm. per liter, plasma proteins were 4.35 Gm., and blood pressure 180/120. A high protein, salt-poor diet was ordered, along with complete bed rest, phenobarbital twice daily, magnesium sulfate by mouth to induce watery stools, and oral hydrolyzed proetin to tolerance.

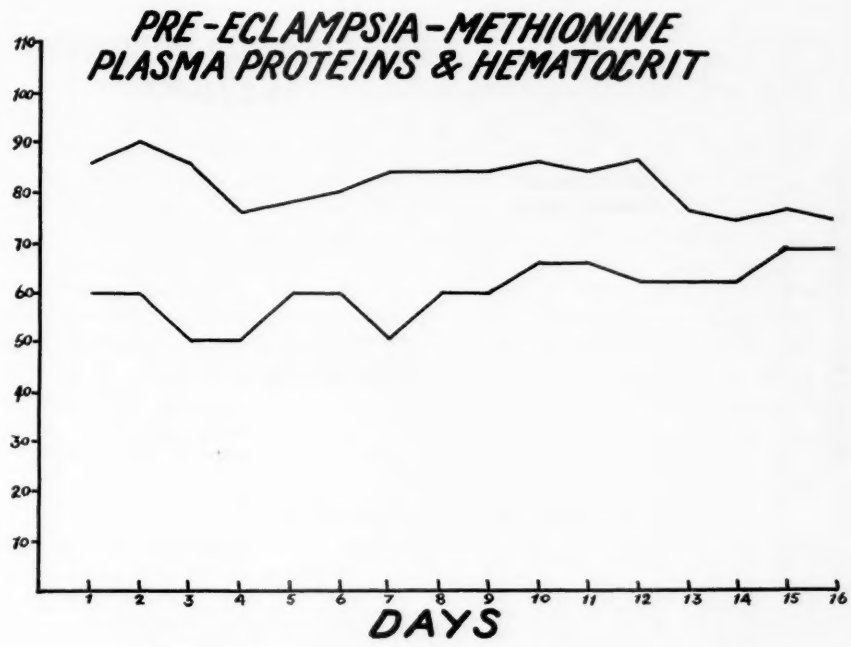

PRE-ECLAMPSIA-METHIONINE
PLASMA PROTEINS & HEMATOCRIT
110
100
90
80
70
60
50
40
30
20
10
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
DAYS

Fig. 8.

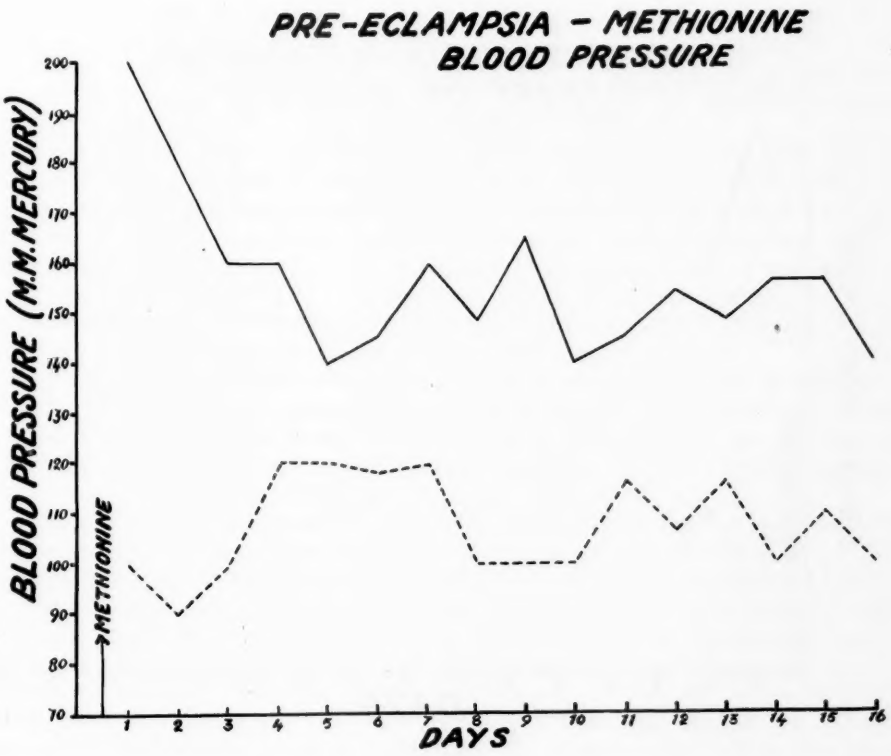

PRE-ECLAMPSIA - METHIONINE
BLOOD PRESSURE
BLOOD PRESSURE (M.M.MERCURY)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
METHIONINE
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
DAYS

Fig. 9.

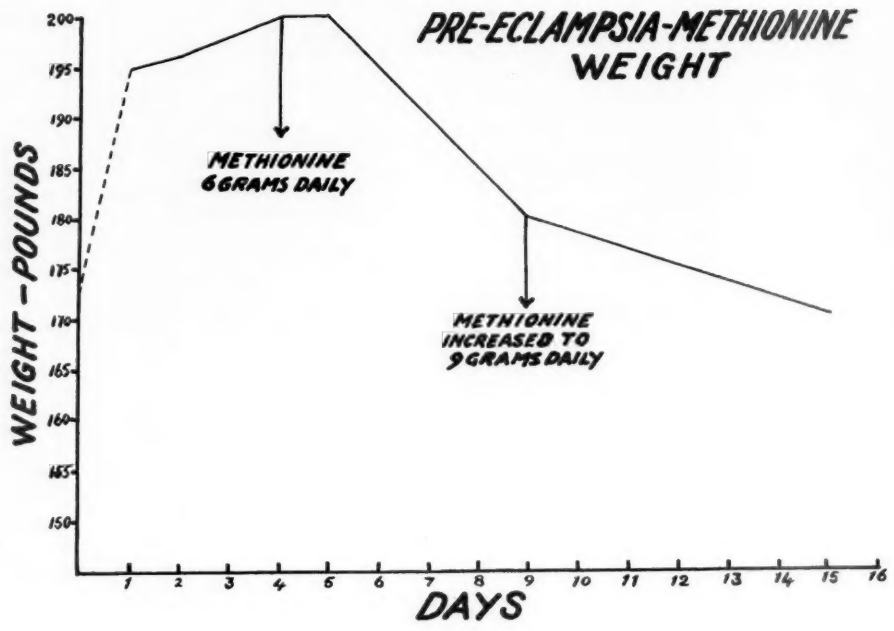

PRE-ECLAMPSIA-METHIONINE
WEIGHT
WEIGHT-POUNDS
200
195
190
185
180
175
170
165
160
155
150
METHIONINE
6 GRAMS DAILY
METHIONINE
INCREASED TO
9 GRAMS DAILY
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
DAYS

Fig. 10.

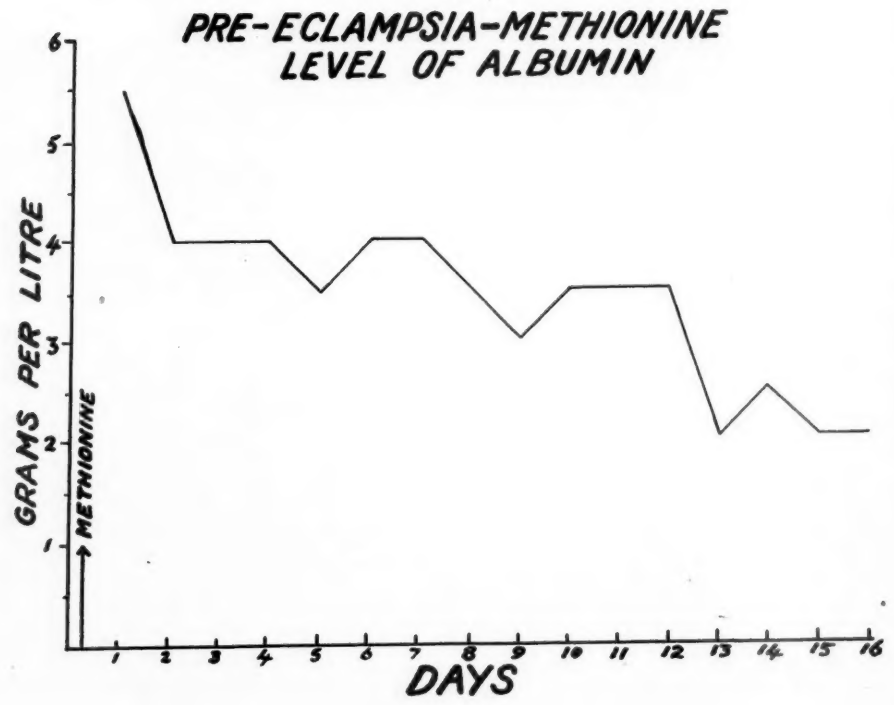

PRE-ECLAMPSIA-METHIONINE
LEVEL OF ALBUMIN
GRAMS PER LITRE
6
5
4
3
2
1
METHIONINE
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
DAYS

Fig. 11.

During the following four days no improvement was observed. On August 27 her blood pressure was 200/130, weight 198 pounds, and albumin 5½ Gm. per liter. The fetal heart tones were normal, but the baby was estimated to be less than 4 pounds. The plasma proteins were 4.25 Gm. per 100 c.c. The urinary output averaged 1,000 c.c. daily.

The hydrolyzed protein was discontinued, and methionine was started, with a daily total dose of 6 Gm. being given by mouth. No other change was made in treatment. During the following twenty-four hours marked diuresis began (Fig. 8) and was accompanied by a steady fall in weight (Fig. 9). The blood pressure did not appear to be affected (Fig. 10). The level of albumin steadily decreased during the course of treatment (Fig. 11). Condition of the mother was excellent clinically, and the fetal heart tones remained regular. The day preceding labor her weight was 171½ pounds, a total loss in two and one-half weeks of 26½ pounds; urinary output was 2,540 c.c.; blood pressure average 160/100, and albumin 2½ Gm. per liter. The plasma proteins showed a gradual, although slight rise to over 5 Gm., and approached the hematocrit levels. Labor was normal, and a living 4¾ pound baby was delivered.

Methods of Supplying Proteins

The use of protein feeding by mouth should be regarded as of major importance. The use of hydrolyzed or predigested protein, orally and intravenously, is becoming popular. A third method, still largely experimental, is the ingestion of certain amino acid components of protein. Evidence produced in animals supports the hope that methionine especially may be proved to be specific in protecting the liver against the ill-effects of protein starvation, or toxic substances.

The ideal diet in pregnancy must fulfill certain requirements. It must furnish protein in biologically valuable form; it must allow such protein to be used by the body for the optimum construction of the fetus, and replacement of wear and tear tissue in the mother; it must be sufficient to allay hunger; it should, if possible, be acceptable to the patient.

Protein itself, unless protected adequately within the body, will be largely broken down and used as a source of energy. When large amounts are given intravenously, approximately 50 per cent is deaminized and used as a source of calories.[35] Several dietary factors conserve nitrogen within the body and prevent such breakdown. If protein intake is high, a sufficient portion will be spared to supply the patient's needs, but, being expensive, cannot be taken in such quantities by the less fortunate group of patients. Furthermore, excessively high protein diets are not well tolerated by many people.

Protein of high biologic value, such as meat, milk, and eggs, is more readily retained. In this sense, vegetable protein is a sparing substance, too, in that it will be deaminized by the body before the more valuable animal protein. This "protein protection of protein" probably explains the good health maintained by people who live on the so-called vegetarian diet.

A third and very important factor is the protein sparing value of carbohydrates, which enhance the storage of nitrogen within the body.[36] Furthermore, the time of ingestion of carbohydrates must be emphasized, for they exert their greatest protein-sparing action only when they are available during the period that the intensity of protein metabolism is at its maximum.[37, 38, 39] This interval is limited to within four hours of ingestion of the regular meal.

Positive nitrogen balance can be maintained by the use of a high carbohydrate, low fat, high protein diet, even with low caloric intake, by the simple maneuver of saving 20 Gm. of carbohydrate from each of the three main meals, and feeding this portion in the midmorning, midafternoon, and evening.[37] There is relief from midmeal hunger, and the decreased physical efficiency seen when the stomach is empty.

Hydrolyzed protein may be administered as a supplement prophylactically, or as a temporary therapy, when digestion or absorption is impaired. Our experiences in this study have left doubt as to the value of such substances in pregnancy. The daily ingestion of large quantities caused no increase in the concentration of plasma proteins over a period of three weeks. It may be assumed that the levels in the normal patients were due to hydration of the blood, the patient was not truly depleted of protein, and therefore added feedings were not necessary. If such an assumption is false, the only other conclusion tenable is that these patients are chronically hypoproteinemic, and prolonged feedings over months would be necessary to increase plasma protein concentration. Hydrolyzed protein is far too expensive to be used in this manner in practice.

No pre-eclamptic patient so treated in this study responded clinically, or had an increase in the concentration of proteins in the plasma before delivery became imperative. Although the patient with eclampsia improved rapidly, she was under strict eclamptic regime with sedatives, and death of the fetus was not prevented.

Methionine is one of the essential amino-acids. It is closely related to cystine and both are sulfur containing. Feedings of cystine-choline or methionine mixtures exert a beneficial change upon a damaged liver.[40]

Liver necrosis, similar to that seen in human eclampsia, can be produced in animals by protein starvation.[40] Such experimental dietary hepatic injury is often combined with bilateral hemorrhagic cortical necrosis of the kidney, seen in human beings only during pregnancy.[41] Both can be universally prevented by the ingestion of protein with high methionine content such as serum albumin, casein, and egg white.

In rats who had developed ascites on a protein deficient diet, a reversal of the condition was obtained by feeding methionine. The first change observed when such therapy was instituted, was marked diuresis similar to that noted in our case.[40]

In pre-eclampsia and eclampsia, several investigators have studied the function of the liver, and have produced evidence to show that impairment exists.[43-52] The toxic hepatitis produced by carbon tetrachloride and chloroform[42] has been benefited in both animals and human beings by the administration of methionine.[53, 54, 55]

Prevention of hepatic injury in human beings requires a daily intake of from 2 to 4 Gm. of methionine or a protein rich diet with a high methionine content.[40] Limitation of fat is essential since it has been shown to aggravate hepatic injury and to prevent the metabolism of protein.

Although experience with methionine in this study has been limited, the observed dramatic changes in weight, edema, and clinical improvement, after five days on usual pre-eclamptic routine had failed, suggest that the results in animal experiments may be hoped for in human subjects. We chose the oral route of administration because it seemed more likely to concentrate the methionine in the liver by way of the portal circulation. Quicker results appear likely when the substance is used intravenously.[41]

Summary

A study of plasma proteins by means of the copper sulfate test upon 600 patients during pregnancy is presented. The effect on plasma protein levels and clinical condition by feedings of protein hydrolysates, and methionine is recorded.

Conclusions

1. The copper sulfate method for measuring the specific gravity of the blood serum or plasma gives satisfactory and clinically accurate estimations of plasma protein concentrations. It is simple, quick, and may readily be carried out as an office procedure.

2. Combined hematocrit and plasma protein estimations give more information than the plasma proteins alone.

3. The hypoproteinemia of normal pregnancy is relative to plasma dilution.

4. Over short periods of time, feeding of hydrolyzed protein by mouth or vein produces no elevation of plasma proteins, or improvement in the clinical condition of patients with toxemia of pregnancy.

5. The hypoproteinemia of pre-eclampsia and eclampsia is very likely due to failure of albumin synthesis by a damaged liver.

6. The essential amino acid-methionine, may, by its protective action upon the liver, materially aid in the prevention and treatment of toxemias of pregnancy. Further experience with its use is necessary.

I would like to express my appreciation to Drs. Paul Guorgy, A. D. Campbell, N. W. Philpott, and J. S. L. Brown for their criticism and help. The oral hydrolysate used was supplied by Frank W. Horner, Inc., the intravenous hydrolysate by Frederick Stearns & Co., and the methionine by Ayerst, McKenna, and Harrison.

References

1. Bruckman, F. S., and Peters, J. P.: J. Clin. Investigation **8**: 591, 1930.
2. Elman, R., and Lischer, G.: Int. Abst. Surg. **76**: 503, 1943.
3. Coetzee, L. J.: Proc. Roy. Soc. Med. **18**: 28, 1924.
4. Dieckman, W. J., and Wegner, C. R.: Arch. Int. Med. **53**: 353, 1934.
5. Dienst: Gynäk. (Archives) **109**: 669, 1918.
6. Eufinger, Heinrich: Klin. Wchnschr. **7**: 492, 1928.
7. Eufinger, Heinrich: Arch. f. Gynäk. **133**: 452, 1928.
8. Plass, E. D., and Bogert, L. J.: Bull. Johns Hopkins Hosp. **35**: 361, 1924.
9. Plass, E. D., and Matthew, C. W.: Am. J. Obst. & Gynec. **12**: 346, 1926.
10. Strauss, M. B.: Am. J. M. Sc. **190**: 811, 1935.
11. Strauss, M. B.: Am. J. M. Sc. **194**: 772, 1937.
12. Strauss, M. B.: Am. J. M. Sc. **195**: 723, 1938.
13. Strauss, M. B.: Am. J. M. Sc. **196**: 188, 1938.
14. Rhinehart, R. E.: Am. J. Obst. & Gynec. **50**: 48-55, 1945.
15. Madden, S. C., George, W. E., Waraich, G. S., and Whipple, G. H.: J. Exper. Med. **67**: 75, 1938.
16. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 3, Baltimore, 1943, Williams & Wilkins, pp. 903-934.
17. Myers, W. K., and Taylor, F. H.: J. A. M. A. **101**: 198, 1933.
18. Meyer-Bisch, R.: Klin. Wchnschr. **4**: 588, 1925.
19. Mussio Fornier, J. C., Castiglioni, C. A., and Anido, J. B.: Rev. Neurol. **1**: 756, 1934.
20. Binger, M. W., and Keith, N. M.: J. A. M. A. **109**: 1, 1937.
21. Rytand, D. A.: Arch. Int. Med. **69**: 251, 1942.
22. Messinger, M. J.: Canad. M. A. J. **55**: 381-383, 1946.
23. Loeb, R. F.: J. Med. **224**: 980-987, 1941.
24. Seeley: Am. J. Physiol. **144**: 369-377, 1945.
25. Weech, A. A.: Bull. New York Acad. Med. **15**: 63-91, 1939.
26. Madden, S. C., and Whipple, C. A.: Physiol. Rev. **20**: 194-217, 1940.
27. Dodge, E. F., and Frost, T. T.: J. A. M. A. **3**: 898, 1938.
28. Strauss, M. B.: Am. J. Obst. & Gynec. **38**: 199, 1939.
29. Phillips, R. A., Van Slyke, D. D., Dole, V. P., Emerson, K., Hamilton, P. B., and Archibald, R. M.: Publication Josiah Macy, Jr., 565 Park Ave., New York.
30. Hock, H., and J. Marrack, Brit. M. J. **2**: 151-153, 1945.
31. Cook, R. P., Keay, D. M., and McIntosh, D. G.: Brit. M. J. **2**: 456-457, 1945.
32. Ebert, R. V., Stead, E. A., Jr., and Gibson, J. G.: Arch. Int. Med **68**: 578-590, 1941.

33. Davis, C. H.: Gynecology & Obstetrics 1: 27, Hagerstown, Md., W. F. Prior, Inc., 1943.
34. Stead, E. A., Jr., and Ebert, R. J.: Am. J. M. Sc. 201: 655, 1941.
35. Elman, R., Lischer, G. E., and Davey, H. W.: Am. J. Physiol. 138: 569-577, 1943.
36. Sherman, H. C.: The Chemistry of Food and Nutrition, ed. 5, New York, 1937, The Macmillan Company.
37. Lovell, M. E., and Rabinowitch, I. M.: Personal communication.
38. Larson, P. S., and Chaifoff, I. L.: J. Nutrition 13: 287, 1937.
39. Haggard, H. W., and Greenberg, L. A.: 1936, Diet and Physical Efficiency (Yale).
40. Guorgy, P.: Am. J. Clin. Path. 14: 67-86, 1944.
41. Guorgy, P.: Personal communication.
42. Miller, L. L., and Whipple, C. A.: J. Exper. Med. 76: 421, 1942.
43. Kaufman, C.: Klin. Wchnschr. 11: 493, 1932.
44. Kaufman, C.: Ztschr. Geburtsh. u. Gynäk. 99: 582, 1931.
45. Botella-Llusia, J.: Arch. Gynäk. 161: 254, 1936.
46. Neuweiler, W.: Klin. Wchnschr. 18: 1050, 1939.
47. Neuweiler, W.: Klin. Wchnschr. 19: 135, 1940.
48. Cross, R. C.: Am. J. Obst. & Gynec. 18: 800, 1929.
49. Herscheimer, A.: Am. J. Obst. & Gynec. 29: 395, 1935.
50. Herscheimer, A.: Am. J. Obst. & Gynec. 37: 363, 1939.
51. Sullivan, C. F., Tew, W. P., and Watson, E. M.: J. Obst. & Gynaec. Brit. Emp. 41: 347, 1934.
52. Hofbauer, J.: Zentralbl. f. Gynäk. 57: 35, 1933.
53. Berryman, G. H., and Bollman, J. L.: Am. J. Physiol. 139: 592-595, 1943.
54. Berryman, G. H., and Bollman, J. L.: Am. J. Physiol. 139: 596-599, 1943.
55. Beattie, J., Herbert, P. H., Wechtel, C., and Steele, C. W.: Brit. M. J. 1: 209, 1944.

Discussion

DR. CANNELL.—Dr. Macarthur has presented results of a very interesting and careful study of plasma proteins in 600 patients. His findings are corroborated in general by many other investigators. To me the principal value of his work is that he has drawn our attention to a simple and accurate method of estimating plasma protein which he tells me, and other biochemists have told me, is quite capable of use as an office procedure. Dr. Macarthur has shown by his paper that this procedure is a useful one which can be adapted to office practice. I feel that anything which will add to our accurate treatment of patients during pregnancy is something that should be drawn to general attention, and he has done that.

From his paper I was not clear whether the relationship between the hematocrit and plasma protein levels preceded the clinical changes which we know as pre-eclampsia, i.e., elevation of pressure, edema, and the other signs. I hope that Dr. Macarthur will clear this up for us. If these findings are found to precede clinical signs by any appreciable time, it is a much more valuable procedure than just an aid in the dietary care of a patient.

He stated earlier that the changes in the liver which are produced by protein starvation are the same or similar to those encountered in the patient dying from eclampsia. I cannot agree that there is any typical picture of eclampsia in a large series of cases. I think that probably about 50 per cent is the maximum number of patients who will show the changes in the liver said to be typical of eclampsia. He has told me that he does not feel that that is of importance in any case, because he is not trying to advance a theory for the cause of eclampsia, but noted that in patients who had a poor protein intake these changes could be induced more readily.

In conclusion, I would like to congratulate Dr. Macarthur on a very excellent presentation, and would urge him to proceed with his studies, particularly with respect to methionine, as it is very interesting.

DR. VAN WYCK.—I believe that thirty years ago it was pointed out that in analyzing the behavior of the serum protein fractions in pregnancy, the shift in the relationship of albumin and globulin was very marked in the toxemias. This was a diagnostic point in the differentiation of eclamptic toxemia from other forms of renal disease in pregnancy. Some years ago Harding noted that in early pregnancy, when the ovum is acting to some extent as a parasite, there was a fall in the serum protein due to the physiologic hydremia,

but that when the patient developed hyperemesis gravidarum, the serum proteins were concentrated, the total figures rising sometimes to 9 per cent, this rise being the measure of acute dehydration. With prompt treatment in an attempt to restore the water balance, the serum protein figures fell back below the prepregnant level as the patient recovered. Harding pointed out, however, that closely recurring attacks of dehydration produced a destruction of these blood substances due to the effort the body made in the contracted and concentrated blood volume to restore the changed viscosity. At first a rapid rise in serum protein followed by a fall and then a rise with a further attack of dehydration, and then a recurrent repetition of this phenomenon ultimately resulted in a low fixed blood protein. Harding regarded this ultimate fixation of the serum protein as a bad prognostic finding. The strange behavior of plasma proteins in pregnancy is now the subject of much investigation, and promises much in the understanding and therapy of toxemia.

DR. EDWIN ROBERTSON.—The point which I should like to hear discussed is one which has not already been mentioned, namely, the specific nature of the toxemia of pregnancy. I am referring to the work of the Smiths in Boston who, some time ago, discovered a toxic factor. The Smiths thought it possible that there must be something in the folklore which points to menstrual discharge being poisonous; they found a highly toxic pseudoglobulin in menstrual discharge similar to that which Menkin had isolated in turpentine-produced pleural effusion in dogs. They also found such a toxic factor in the blood of women suffering from toxemia.

I wonder whether, in his study of toxemia, Dr. Macarthur has taken cognizance of the Smiths' work on the subject.

DR. PHILPOTT.—I believe that perhaps the most important contribution that will be made in the treatment of toxemia and eclampsia might be in this direction. We do not know much about the causation of toxemia today, but we struggle with many causes. There is a very definite relationship between toxemia and low plasma protein. We have had in the last two years several cases that have responded very well to different forms of supplementary protein administration. One case under study had a very low plasma protein, 3 Gm. per cent, and was treated with plasma transfusion. Three transfusions of 250 c.c. each were given in four days. At the time of her first transfusion blood pressure was 200, eyes were almost closed with edema, and the patient looked as though she were head for a convulsion. With the first transfusion the symptoms started to disappear, and with the third she was normal with reference to the edema and blood pressure. The patient was carried along for some time and she was delivered a few weeks later of a normal baby. She showed no sign of toxemia at the time of delivery.

I believe there is a great future with Methionine. It is used in our clinic for post-operative cases in shock and has been managed by Dr. Browne with excellent results. We find it a most beneficial way of treating cases of suspected or definite liver damage.

DR. MACARTHUR (Closing).—In reply to Dr. Cannell, I must say that we have as yet not established the value of the hematocrit-plasma protein test in the early, subclinical, toxic woman. The source of my impression regarding hypoproteinemia is mainly the work of Guorgy, who has shown that prolonged protein starvation in animals causes necrosis of the liver identical to that found in human eclamptics, often combined with bilateral cortical necrosis of the kidney.

We have not used plasma in the treatment of toxemia, chiefly because it is difficult to obtain, and protein hydrolysates are much cheaper, although perhaps not as physiologic.

I freely admit, with Dr. Robertson, that many interesting hormonal theories have been elaborated, to explain pre-eclampsia and eclampsia. Liver damage may not explain this complex disease, but may be an important link in the chain. Perhaps by its adequate protection we may go far in finding the solution.

I would refer Dr. Puddicobe to the articles of Phillips and others in which they give the complete technical details of plasma protein, serum protein, hematocrit and hemoglobin, and red cell counts. Their directions are sufficient to enable anyone to carry out this test in the office.

A STUDY OF MATERNAL MORTALITY IN CANADA*

MARION KERR, M.D., TORONTO, ONTARIO

DURING the last ten years the maternal death rate for Canada has shown an encouraging improvement. In 1934 the rate was 5.3; 1936 to 1940, 4.6; 1941, 3.5; 1942, 3.0; 1943, 2.8; and 1944, 2.7. We owe this steady improvement to several factors, such as better hospital facilities and the increased desire on the part of patients to seek hospitalization, improved obstetric technique, and the many prenatal services now available, with the education of the lay public of their value. The use of blood and plasma, the sulfonamides, and penicillin have all contributed to the reduction of maternal mortality. The improved methods of anesthesia and the more efficient methods of relieving the pain of labor have also reduced the number of fatalities.

In 1934 there was a range in the maternal mortality rates for the provinces from 4.1 to 2.3, and in the rates for larger cities of 40,000 population and over, from 5.9 to 1.0. The range in 1940 for the provinces was from 4.8 to 2.9, and for cities of 40,000 population and over, 7.0 to 2.1.

In the study of statistics of the past ten years, the chief causes of death of puerperal women are infection, toxemia, and hemorrhage, and in the order stated. In 1939, 72.6 per cent of all maternal deaths were due to these causes: septicemia, 32.1 per cent; toxemia, 24 per cent; and hemorrhage, 16.5 per cent. In 1934 401 women died of septicemia and septic abortion. In 1944 there were 265 women who died from these causes. Although there has been this marked decrease in the number of deaths from sepsis, it still remains the most frequent cause of maternal mortality.

Many of these deaths may be deemed preventable, and the prevention is chiefly the responsibility of the physician. The causes of puerperal sepsis are found to be prolonged labor, anemia, or blood loss, cesarean section, and operative obstetrics. Prevention is accomplished only by good obstetrics. Deaths from septic abortions, of which there were 85 in 1944, are included. These cases are a problem unrelated to maternity for which the profession is seldom directly responsible. The medical profession, however, should lead the way in finding a means of preventing these deaths from septic abortion.

In 1934 toxemia, the second greatest cause of maternal mortality, was responsible for the loss of 260 mothers.

In 1940 mortalities from this cause numbered 234, or 23.9 per cent. In 1941 toxemia was the largest single cause of maternal deaths accounting for 222, or 24.7 per cent. In 1942 the rate was 22 per cent; 1943, 20.3 per cent; and in 1944 it had fallen to 15.7 per cent.

*Presented at the Second Annual meeting of the Society of Obstetricians and Gynecologists of Canada, Ste. Marguerite, Quebec, Oct. 27-29, 1946.

The promise of still greater improvement will depend upon close supervision of all pregnant women, and the earliest possible recognition of the actual appearance of toxemia. The causes of the toxemia of pregnancy are still unknown, and the prophylaxis is still better than cure. Good prenatal care, increased hospitalization of pregnant women, and prompt institution of bed-rest treatment of even the mildest case of toxemia will give us improvement. Prevention of the occurrence of eclampsia in a nonconvulsive toxemic patient by proper medical management is of paramount importance. The mortality of the convulsive toxemias is eighty times as great as the nonconvulsives.

The accuracy and value of statistical deduction depend upon the quality of the information furnished by the certificate of death. The figures for 1941 to 1944 were compiled according to the fifth revision of the *International List of Causes of Death* and are not strictly comparable with the figures for 1940 for individual causes. Obstetric death is commonly the result of several causes, rarely one, and actually it is very often impossible to assign death to one cause.

It has been said for many years that infection as the most common cause of maternal death is the most important. Hemorrhage is no doubt far more common everywhere than indicated by its statistical frequency, and it is the outstanding controllable factor. Preventive measures for reduction in maternal mortality will produce greater results if we place emphasis on hemorrhage rather than infection. At present hemorrhage is the most important cause of maternal mortality, and probably the most common as well. In a study of the Maternal mortality statistics of the United States for 1941 and 1942, it was found that in 1942 there was a 10 per cent reduction in the deaths due to infection, an 11 per cent reduction in deaths from toxemia, but practically no decrease in the number of deaths from hemorrhage. In Canada there has been little, if any, improvement in maternal mortality from hemorrhage since 1931, when there were 137 deaths from hemorrhage. In 1940, maternal deaths from hemorrhage numbered 138, comprising 14.1 per cent of all maternal deaths. In 1942 there were 155, comprising 17.2 per cent. In 1943 there were 170 deaths from hemorrhage. In fact, hemorrhage was the largest single cause of maternal mortality, 21.3 per cent.

Undue loss of blood is to a great extent preventable. Hospitalization of every women who bleeds during her pregnancy, and routine blood studies with blood typing and the determination of the Rh factor are essential. Many of the obstetric complications are influenced by hemorrhage. In the early months of pregnancy ectopic gestation and abortions are the chief causes. Later in pregnancy placenta previa and abruptio placentae cause the serious hemorrhages. In the delivery, trauma and the placental stage are the main causes of death from hemorrhage.

Proper conduct of the second stage of labor and conservative management of the third stage will reduce materially the deaths which are directly due to hemorrhage, and will also enable the puerperal woman to combat complications, particularly infection and toxemia, which might otherwise prove fatal.

If excessive blood is lost, it should be replaced as soon as possible and in sufficiently large amounts. Blood is the puerperal woman's most powerful ally but if not immediately available, plasma is now procurable in even all outlying districts. We have become aware of its lifesaving qualities in cases of shock, yet more and more it becomes apparent that plasma will not save life if the blood loss has been great. Some method whereby hospitals can get blood replacement easily, cheaply, and promptly is very important. If veins cannot be entered, bone marrow infusion through the sternum is a procedure which should be used.

According to the statistics of the Chicago Lying-in Hospital, heart disease has been one of the major causes of maternal death. Our Canadian statistics of maternal death do not list death from cardiac disease. The rate of mortality from phlegmasia alba dolens, embolism, or sudden death does not run a parallel course with sepsis. An almost steady rise occurred since 1934, ending with a definite peak in 1940 with 156 deaths. The rates for all other conditions except accidents were the lowest in that year. The rate in 1944, however, was the lowest ever recorded—seventy-six deaths.

Under the heading of other accidents of childbirth are included cesarean operations, other surgical operations, instrumental deliveries, dystocias, ruptures of the uterus in parturition, together with other or unspecified conditions of the puerperal state, as puerperal diseases of the breast, etc. In 1940, ninety-nine deaths were attributed to these causes, which was 8.3 per cent. Since 1936 there has been a steady decrease in these numbers. The use of blood and plasma has decreased the number of fatalities from cesarean section. The careful selection of cases, improved preparation, better methods of anesthesia, and the lower uterine segment type of operation has made it a safer procedure.

The prevention of maternal mortality should begin in childhood. In the prevention of rickets, tuberculosis, syphilis, and the acute communicable diseases of childhood, we are laying the foundations for a healthier motherhood. The growth and normal development of girls are dependent largely upon proper nutrition, freedom from infections, and suitable exercise. It is well known that rachitic pelves, damaged hearts and kidneys, and chronic foci of infection increase the risks of pregnancy. Health should be regarded as a major objective of modern education. In all secondary schools ample provision should be made for mothercraft classes to be instructed by well-trained and experienced public health nurses. These should be made compulsory for all girls. They would be better equipped for motherhood, would also have a fund of knowledge which would help them to meet the broader problems of social hygiene. Another important factor in the reduction of maternal mortality is the puerperal woman herself. The ability to choose a skillful physician, a competent nurse, and a well-equipped hospital are of vital importance. Her capacity to grasp and to carry out simple hygienic rules and her "teachability" as to the importance of symptoms and signs, which indicate approaching danger, are large factors.

A well worked-out program of parental education should be available in every community in which parent-teacher associations, women's clubs, etc., should be encouraged to take an active part. Prospective mothers of all grades of

intelligence and of all social classes will take advantage of instruction for expectant mothers, if presented by thoroughly trained and experienced public health nurses.

This instruction should be made available to all prospective mothers and fathers, regardless of their economic condition.

If 85 per cent of the maternal deaths are preventable as one obstetric authority states, the time is ripe for action. Judging by accomplishment in other fields, a *"Canadian Safe Motherhood Association"* or some such name would serve to crystallize the energy awaiting leadership. Obstetric authorities are prepared to give expert advice; public health workers are accustomed to organize and promote, and the informed public will furnish the financial support.

Medical and hospital care should be supplemented by education of the public, through the work of public health nurses, the press, radio, and other media, regarding the need for, and value of, good maternity care. The public should be instructed as to the proper diet and hygiene for the mother during the maternity cycle. There can be no question that well-equipped maternity hospitals with skilled staffs, using conservative methods of treatment, are the safest places in which to have a baby. In Canada, one of our great needs is increased hospital accommodation. It is estimated that only 47 per cent of pregnant women in Canada are able to be delivered in hospitals. To assure maintenance of adequate hospital maternity services in any community, hospitals must not be dependent upon charity contributions and upon the extra charges of private patients to meet the loss through its free services. Any approved hospital should be supported from public funds on a cost basis for providing all in-patients maternity care, the cost of maintenance of facilities for the prenatal care and all laboratory and x-ray services. The maternity patient administration is a community responsibility, and a larger provision should be made from public funds.

We do want to have the best maternity care for all mothers that it is possible to provide, so that Canada will be a place of safe motherhood.

Discussion

DR. PHILPOTT, Montreal.—Dr. Kerr has shown very ably today that hemorrhage is the greatest killer, and that it is preventable. We shall prevent it only by comparing results in various clinics. I would like to exchange statistics with Toronto, Winnipeg, and Vancouver. We could learn a great deal.

I am sure that in our clinic (Victoria Hospital of Montreal) today half of our patients who die could have been saved had they had adequate treatment. In a society such as this we could go forward in a concentrated effort to organize the management of obstetric patients. We should have some system and recommendations to offer to general practitioners and the public whereby each individual doctor will fit into his proper place. I think, as Dr. Sanche said, that many general practitioners do not have the right facilities, and specialists are at a disadvantage in having to handle patients that are tragedies before they see them. A plan whereby general practitioners would handle certain types of cases, others to be handled by specialists, and still others handled in hospitals would be advisable. It is the obligation of this society to make this endeavor.

DR. HECTOR SANCHE.—This ten-year analysis of maternal mortality in Canada is of pre-eminent interest, and the steady improvement it has shown, improvement which goes on in 1945, whose maternal death rate has been 2.3, is an encouragement to the medical profession.

Although there is a considerable improvement as a whole, each of the eleven headings under which deaths from puerperal causes are classified do not mark great percentage changes in regard to the total.

The three chief causes of maternal deaths are always septicemia, toxemia, and hemorrhage, and in the order stated; they stand for 70 to 75 per cent of all deaths. Septicemia has kept approximately its same percentage, toxemia has improved, while hemorrhage has increased.

Dr. Kerr has stated as factors of improvement: better hospital facilities, increased desire on the part of patients to seek hospitalization, improved obstetric technique, prenatal services, use of plasma, sulfonamides and penicillin, and has emphasized the development of these factors to a higher level.

Three parties are interested in the improvement of the maternal death rate: the medical profession, the patient, and the public. All three must cooperate if we want to get better results.

I can say that the medical profession as a whole is always looking for better standards in medical care. But we cannot bring for comparison specialists who work in favorable conditions, who are ready and able to improve their obstetric technique, and the general practitioner.

All hospitals will tell us that their maternal death rate is brought higher than it should be, not from their booked cases, but from their emergency cases. What does this mean? That the medical care is not of the same standard inside and abroad. And why? Because the factors mentioned above are not found at the same level here and there.

If we want to keep on the downward grade of the maternal death rate, we must continue the work in hospitals, but we must also help the general practitioner and enable him to share the benefit of our work, both in researches and facilities.

Most of us are teachers in our different communities, and we are aware of what our students know when they leave the University. They are well enough equipped to look after normal obstetric cases, but how many eclamptic patients have they seen, how can they handle a case of dystocia? And I would add, when will they be able to handle these properly if we admit that they attend fifty to sixty maternity cases a year, and when we know that severe dystocia or pathologic cases are sent to a far-off hospital where they cannot be associate with the delivery, and perhaps hear about the treatment only by the patient's own report.

The patient's cooperation consists in having her come to the doctor's office or to the clinic for medical supervision first, and second, in having her convinced of the importance of the directions she is given.

The increased desire on the part of patients to seek hospitalization is actually curtailed by the hospital facilities. Live births in institutions have increased from 39 to 60.9 between 1938 and 1944, and this increased demand has created shortage of hospital beds. On the other hand, when birth in an institution is mentioned, "institution" does not necessarily mean a well-equipped hospital.

We should also bear in mind that 90 of 798 mothers died in 1943 without having a doctor in attendance, that is 11.3 per cent. This fact may come from two causes: (a) neglect on the part of the patient, (b) scarcity of doctors.

The cooperation on the part of the second party will be obtained inasmuch as the third party, the public, is aware that pregnancy is a matter that should be prepared and looked after, and that it is now recognized that prenatal hygiene, prophylaxis, and medical attendance will save many mothers' lives.

And here I agree with Dr. Kerr's recommendations that the prevention of maternal mortality should begin in childhood, that parental education, and that the education of the public should be done through the press, radio, and all other possible media.

Well-equipped maternity hospitals with a skilled staff is surely the safest place to have a baby. These hospitals should be disseminated on a larger scale in different centers throughout the country, so that one of them be within easy reach of every practitioner. There the isolated medical man in the country could take his patient to get treatment, if necessary, or to seek advice from a skilled specialist for further treatment at home, without having to lose days of his own time.

Before closing this discussion, I would like to set forth an idea. It is timely to discuss maternal mortality. It has been said that 85 per cent of maternal deaths are preventable; I agree, and they would be prevented if—but there will always be so many ifs—that, it is my opinion, the maternal mortality rate is not likely to come down a great deal more. This is no reason to give up in despair.

But it would be of paramount importance to take more interest in maternal morbidity (morbidity during the puerperium) and permanent invalidity to any degree. So many mothers are crippled, I dare say, to a certain extent after one or several pregnancies. Would it be possible to have a uniform base of obstetric morbidity all over the country, to establish statistics in this regard? In this way we could see the end results of our obstetric work, not only inasmuch as those who die, but inasmuch as they live and go through pregnancies curtailed in health, in their vitality, and in their potential in regard to themselves, their family, and the nation.

And I believe that this society comprised of obstetricians and gynecologists is the organization that should set forth this idea throughout Canada.

DR. FRASER.—There are one or two points I would like to bring up. Dr. Kerr has very ably presented the picture as it exists in Canada and elsewhere. I have always had the feeling that one of the greatest weaknesses of our present system lies in our failure to provide the average pregnant woman with the same type of treatment and care that we give the prospective surgical patient. Over the years there has been developed widely a place for the preparation of a woman for operation. Nothing is considered extravagant in the way of examination of treatment prior to the event, yet the average pregnant woman who is about to undergo a surgical procedure receives very scanty consideration. Often a woman approaches delivery with a hemoglobin of 50 to 60 per cent—sometimes less, far below the level considered necessary for a surgical operation. It is possible and should be regarded as essential that the hemoglobin level in pregnancy be maintained at or near 100 per cent. *What then is required is the provision for each and every pregnant woman of a sound and complete medical examination?*

In the report of the *British Committee on Maternal Mortality* tabled in the House of Commons in 1932, in which a very large series of Maternal deaths were analyzed, it was possible to recognize two large groups of cases: (1) those where death was due to childbirth, directly; (2) those where death was indirectly due to childbirth. In group 1 sepsis played a leading role. It was shown that the occurrence of sepsis over the previous hundred years displayed about the same incidence. Reports from Ottawa show the high incidence of sepsis in the causation of death from childbirth. I wonder if we are convinced of the importance of nasopharyngeal infection (active or latent) in those in attendance on pregnant women? Colebrook and his group in London have shown clearly the possibility of transmission of infection from this source and, indeed, have been able to trace the source of infection in many cases to this region. *Sporadic outbreaks* of infection in maternity hospitals may in this way be explained. It is essential that women be delivered in an environment free of infection. Masks should be worn by all those in attendance, and it is possible that some of us by reason of chronic nasal infection may not be able to undertake this special work.

A Final Suggestion.—We have learned much from the preparation of five-year reports on the results of examination, classification, and treatment of cancer of the uterus, particularly the cervix. By study of individual cases, methods of diagnosis and treatment, and as the result of comparison with the results of other observers, progress of a sound type has occurred. I would therefore suggest that a similar procedure be adopted in obstetrics: each hospital where deliveries take place should annually prepare a statement of the year's

work, giving a clear picture of the types of cases dealt with, the treatment given, and the end results. In addition, it would be of the greatest value if each year a report could be attached giving the particulars of diagnosis and treatment in some special group of cases over the previous five years. For example, this year a survey would be made of results in the management of all types of toxemia, next year possibly hemorrhage could be dealt with. In such a way over a period of years there could be available a vast amount of information pertaining to the treatment of all of the important complications of childbirth in Canada. Such information is not yet available in the literature, and so, if we in Canada could initiate such a plan, real progress would be made.

DR. VAN WYCK, Toronto.—The steadily falling maternal mortality rate in our country is a matter of great gratification. There are really three causes of maternal mortality—ignorance, poverty, and neglect. Poverty we can do little about. Neglect rarely plays a part. Ignorance applies not only to the profession, but to the patient. It is fitting that a society of this kind should undertake a program to consider maternal mortality, but the examination of large masses of statistics, while they have value, are not as important as careful analysis of individual tragedies. There are places in the United States where each maternal death is subject to scrutiny by a committee. It would be well to have committees set up locally and subject these individual tragedies to analysis. The ultimate solution is the education of the profession. This should be done, not in a critical manner, but with a view to clearing up the ignorance of both profession and patient. I believe that this society by a Maternal Welfare Committee could advise the proper authorities in this matter, and that such guidance would be a great step forward.

DR. KERR (Closing).—From Dr. Van Wyck's discussion it would be a very splendid thing if this organization would set up a committee on maternal mortality. It is done in various cities in the U. S. where committees study all maternal deaths.

VAGINAL REPAIR COMBINED WITH VAGINAL HYSTERECTOMY*†

J. E. HARRISON, M.D., C.M., VANCOUVER, B. C.

IT IS not intended herein to divulge some novel or simplified surgical procedure for vaginal repair with vaginal hysterectomy in varying degrees of prolapsus. Rather it is hoped to focus attention upon a sound operation which presents distinct advantages over certain other treatments of this affliction, and yet which is not commonly applied. It is felt that from experience gained through even a relatively small series of cases one might point out a few helpful ideas in a technique which, to be consistently successful, must be meticulous. Most of the literature on this subject to date lacks detail in description and passes over some of the important as well as some of the most difficult steps in the operation as if they did not exist.

Time will not here permit detailed discussion of anatomic considerations. The recent publication "The Pelvic Floor in Parturition" by Richard Power of Montreal, in *Surgery, Gynecology and Obstetrics,* September, 1946, treats this portion of the subject so well that one could do no better than to recommend its careful perusal. Suffice it to mention here the supporting pelvic structures which one must be familiar with, in order to reconstruct properly a broken-down pelvic floor after vaginal hysterectomy.

First.—The endopelvic fascial diaphragm or upper pelvic fascial floor, composed of (a) an anterior segment or pubocervical layer, representing the platform which supports the bladder; (b) the strong lateral segments or condensations, known as Mackenrodt's ligaments, or the lateral ligaments of the cervix; (c) the posterior segments or condensations known as the uterosacral ligaments. All three of these segments having attachment to pelvic bony structure, and to a definite fibrous fascial capsule, forming a collar about the supravaginal cervix. The rectovaginal septum is an extension of this capsule which descends caudally from its posterior margin, between vagina and rectum to terminate in the perineal body.

Second.—The smooth muscle diaphragm in the base of the broad ligament, lying between the endopelvic fascial diaphragm and the upper surface of the levator ani muscle. Smooth muscle bundles radiate from the uterus at the level of the internal os, imbedded in fibrous tissue below the upper pelvic fascial floor, and enter into the composition of the ligaments just mentioned.

Third.—The levator ani muscular diaphragm, whose anterior segment, the pubococcygeus muscle, forms the largest, strongest, and thickest part of the pelvic floor.

Fourth.—The urogenital diaphragm, composed of two leaves of fascia and containing mainly the sphincter urethrae, and deep transverse perineal muscles.

Fifth.—The sphincteric muscle group, whose action is only very slightly supportive.

Sixth.—The perineal body, whose importance in this connection is because each one of the diaphragms constituting the pelvic floor has an insertion into it.

*Presented at the Second Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, Ste. Marguerite, Quebec, Oct. 27-29, 1946.

†For lack of space, it is not possible to include all of the illustrations submitted, but only those showing the essential features of the operation.

Seventh.—The broad and round ligaments, which in their usual position admittedly have little or no supportive action, but which after vaginal hysterectomy, may be employed as a very real support both for the bladder and the vaginal vault.

Uterine prolapse and cystocele following childbirth are the results of stretching or tearing, or both, of the endopelvic fascial diaphragm, and the smooth muscle diaphragm, from their attachments to the uterus and bladder. In cystocele, the pubocervical segments of these diaphragms beneath the bladder may be split in the midline between cervix and pubis. The degree of herniation and prolapse depends upon the extent of the injury, the position and weight of the uterus, and varying degrees of intra-abdominal pressure, but it is facilitated by stretching or tearing of the muscular levator diaphragm which in turn enlarges the outlets below.

If in addition, the urogenital diaphragm, sphincteric muscle group, or the perineum be extensively lacerated, the uterus can prolapse to a still greater degree. Stretching or tearing of the rectovaginal prolongation of the endopelvic fascia completes the picture of prolapse with rectocele and possibly enterocele.

Advantages of Vaginal Hysterectomy in the Repair of Procidentia

Adequate reconstruction of the pelvic floor demands recognition and repair of all damaged structures; at the same time removal of irreparable, diseased, offensive or potentially troublesome tissues is indicated.

It is not enough, one would readily admit, to do an anterior colporrhaphy and a perineorrhaphy in a case of prolapsus. It is not enough to do as well an amputation of the cervix—even a high amputation. It may not be enough, either, to supplement these by bringing the lower portion of Mackenrodt's ligaments together in front of the amputated cervix, or even overlapping them with one or two sutures, especially if the uterus is large and the ligaments are poor. If high rectocele or enterocele or both are present, they must also be dealt with, and too often the repair of the upper posterior vagina is neglected.

Vaginal hysterectomy proffers ease in the complete management of all conditions related to prolapse. The sagging uterus is removed, giving free access to all the supporting structures possible: the uterosacral ligaments; the entire depth of the lateral cervical ligaments, with their lower smooth muscle and upper strong fascial components; the frequently thick and strong upper broad and round ligaments which may now be used as definite aids in supporting the new pelvic floor as well as the bladder. And finally, in the presence of enterocele or high rectocele, no other operative procedure can give equal exposure for their rectification.

One occasionally hears the opinion that the uterus is better left in, to act as a central supporting hub to which the stretched ligaments may be fastened. Yet do we worry about the vaginal vault when total abdominal hysterectomy is done? And is it not true that besides restoration of the pubocervical fascia, the main support usually given when vaginal hysterectomy is not performed, consists of one or two sutures, drawing the lower parametrial tissue together

in front of the cervix? With vaginal hysterectomy all ligaments are shortened as indicated by the degree of prolapse, their stumps are firmly united on each side and then to their fellows on the opposite side. They are anchored securely to the subpubic fascia beneath the urethra, and finally the anterior vaginal wall is made fast to them. The ultimate effect, without the previous downward pressure of the sagging uterus, is that the contraction and shortening of the ligaments actually lift up the anterior vaginal wall and the vault.

Vaginal hysterectomy with repair is to be recommended in preference to high amputation of the cervix in any case, first, because with poorer exposure and subsequent reconstruction of the cervix there is more likelihood of damage to ureters, and second, because if the patient is in the childbearing age there is danger from future pregnancy.

There are also distinct advantages in this procedure over the method of vaginal repair plus abdominal hysterectomy in cases where removal of the uterus is indicated. There is less risk of injury to ureters and bladder, less risk of peritonitis, postoperative ileus or shock. In the fat or aged or debilitated patient it may be done easily and without shock under local anesthesia.

The advantages of vaginal hysterectomy over Watkin's interposition operation are self-evident. The latter does nothing which the former cannot accomplish, and of course leaves in an abnormal and awkward position a uterus which may become troublesome.

The operation for vaginal repair plus abdominal ventrofixation of the uterus needs mention only for condemnation as unsatisfactory and as an unnecessary hazard for the patient. Too frequently the surgeon who does this type of operation depends upon the fixation of the uterus to correct the prolapse, and so does an incomplete repair of the vagina. Many of these cases appear later with a recurrent cystocele or enterocele, and yet the cervix is held so high by ventrofixation that proper vaginal repair, alone, is impossible.

The patient who has had two or three repairs, and still has prolapse, is an ideal candidate for vaginal hysterectomy. Here one has access to an unused set of supporting structures, in place of old ones attenuated by repeated dissection and scarring.

Disadvantages

Vaginal repair with vaginal hysterectomy is definitely a more difficult and painstaking procedure than others, but if one familiarizes oneself with the technique it is not more dangerous, and in many instances is less dangerous. It is more time consuming excepting the case where repair and abdominal hysterectomy are done, but if the time consumption be not fatal to the patient, this should not be considered in comparison to the many other advantages. We all do the more difficult and longer operation of total abdominal hysterectomy rather than subtotal, because we believe it is a better operation for the patient.

One hears that it is bad physically and psychologically for a woman to lose her uterus, and with it her menses. Excepting the young woman who has not yet completed her family, and therefore of course, where the operation

should not be considered, this argument does not face the light of fact. On the contrary, one is almost invariably impressed in cases of prolapsus, not only by the sense of physical well-being, but by the sense of mental relief which follows removal of the so-called offending organ.

Occasionally after repair with vaginal hysterectomy the patient is left with too short a vagina. Many of these cases are in the older age group to whom this complication is usually unimportant. It happens chiefly in the patients with complete sacropubic hernia, and in these instances one is likely to finish any type of operative procedure with a shortened vagina. In the younger group where the vagina is not already contracted, it is rare if certain principles in technique are adhered to.

Indications for Vaginal Hysterectomy With Vaginal Repair

Under this heading come first the group of women who are at or near the menopause, who have badly ulcerated tissues, severe bleeding, or irregular spotting, all of which arouse anxiety or fear of cancer. Even for the gynecologist and/or the pathologist, it is not always easy to exclude cancer by biopsy, either grossly or microscopically. In this age group also severe dysmenorrhea may logically be considered an excuse for hysterectomy when vaginal repair is done. The patient is relieved at once of a painful or bleeding organ.

In this and older age groups, where cervical cystic disease or hypertrophy indicates amputation of the cervix, is it not sound judgment to remove the whole organ, and thereby exclude the possibility of subsequent fundus cancer? We all apply this same principle in our modern concept of proper procedure in abdominal hysterectomy, and although admittedly cancer of the cervix is more common than cancer of the fundus, the latter is nonetheless a real hazard.

In women past the menopause it would seem too, apart from the advantages in repair of prolapse, that for the same reason, a logical prophylactic measure would be to remove an organ which is beyond physiologic usefulness.

In the younger age group other indications to be considered are cases of fibromyoma of the uterus, adenomyosis, intractable severe bleeding, and perhaps some instances where sterilization is deemed necessary.

A very real indication for vaginal hysterectomy with vaginal repair are those cases on whom previous inadequate repair has been done, with abdominal fixation of the uterus, and where there has been subsequently, recurrence of vaginal prolapse with the cervix remaining high. In these cases the uterus must first be released by laparotomy, followed by its extirpation through the vagina with proper restoration of the pelvic floor.

Contraindications

Removal of the uterus in the course of repair is definitely contraindicated in the younger women who have not yet completed their families. The other contraindications are fixation of the uterus or adnexa by old inflammatory disease or endometriosis, and intraligamentous or retroperitoneal growths or previous operations which might complicate procedure.

Technique

If the operation is performed under anesthesia other than local, blood loss may be greatly diminished by preliminary injection of one-half cubic centimeter of pituitrin into the lower parametrium on either side.

The anterior lip of the cervix is pulled well down with volsellum forceps, and the anterior vaginal wall incised transversely just above the point at which it becomes fixed to the cervix. If incision is made below this point, one may have difficulty in identifying the vesicocervical ligament, through which entrance is easily gained to the space between bladder and cervix. The incision is carried through mucosa and fascia, so that it will gape widely with upward retraction of the vaginal wall, and expose clearly the juncture of bladder and cervix. To further improve exposure one may dissect the anterior vaginal wall from the underlying bladder with curved blunt-pointed scissors, upwards for an inch or so, dividing the freed wall in the midline and retracting the mucosal edges. This will give full view of the vertical fibers of the vesicocervical ligament, which separates the vesicocervical from the already opened vesicovaginal space. The ligament is grasped with toothed thumb forceps, lifted up to appear as a sagittal fold (Fig. 1), and is incised with scissors held tangent to the surface of the bladder midway between bladder and cervix. This opens the vesicocervical space from below much more accurately than can be done with blunt gauze dissection. With traction downward on the cervix, first one index finger and then both are slipped up into the loose connective tissue beneath the bladder (Fig. 2) to separate the attachments between bladder and uterus completely. One not only reaches upward as high as possible, but separating the fingers widely, pushes laterally to free the base of the bladder and the ureters from the broad ligaments beneath.

The cervix is next pulled toward the symphysis, a posterior weighted speculum holding the vaginal tissues toward the sacrum. A transverse incision is made through mucosa and fascia of the posterior vaginal wall at the same level as that already made in the anterior wall. This incision may not overlie the tip of the pouch of Douglas, especially if the cervix be hypertrophied and elongated, but an incision made further down the posterior wall than this would shorten the vagina accordingly, and should be avoided. One may divide the wall vertically in the midline from this point downwards until the peritoneum is reached, and remembering the proximity of the rectum to vaginal wall, the opening into the peritoneal cavity should be made close to the uterus. The peritoneum of Douglas' pouch is incised transversely, and its lower margin made fast with a suture to the adjacent margin of the vaginal wall. A wide posterior speculum is then slipped into the pouch of Douglas, and, if omentum or bowel is seen, the head of the table is dropped to carry them up out of the operative field, or a taped sponge is placed within the cul-de-sac. If unusual difficulty is encountered in finding the peritoneum of the cul-de-sac, due perhaps to obliterative adhesions within, the uterovesical pouch of peritoneum is opened and a finger is carried down behind the uterus to push the cul-de-sac forward through the posterior wall incision into plain view.

The ends of the anterior and posterior vaginal incisions are joined by lateral incisions through mucosa only, and the upper leaf of the mucosa on either side is pushed with gauze well up to the level of the internal os. Superficial fibres of the lower parametrium are snipped and also pushed up, to carry a possible vagrant low-looping ureter out of harm's way.

A wide retractor is now placed beneath the bladder in the uterovesical space (uterovesical peritoneum still unopened), and, holding the bladder well forward, the cervix is pulled posteriorly and to the patient's left, thus drawing the right ureter well away from the uterus.

The left index finger is carried through the cul-de-sac opening behind the right uterosacral ligament, to a point above it and close in to the uterus. Having decided how much tissue is to be ligated, depending upon the thickness and depth of the uterosacral and lateral cervical ligaments, a crushing clamplike heavy Oschner forceps is applied for a moment to thin out and groove the tissue. This is removed and replaced by a ligature of No. 2 chromic catgut, carried through by a ligature carrier from the anterior surface of the parametrium, to the tip of the index finger close to the uterus in the cul-de-sac. A small but useful point in the tying of fairly large "bites" of parametrial tissue is that the assistant should relax his pull on the cervix as the knot is made. Otherwise tension on the tissues will prevent a securely fastened knot. The crushing of the tissue first also makes possible a more securely tied ligature, and the grooving insures against subsequent "slippage." The ligature is held long and the parametrium and uterosacral attachment is divided at least one-fourth of an inch distal to it. Provision of a generous stump distal to the ligature also prevents ligature "slippage."

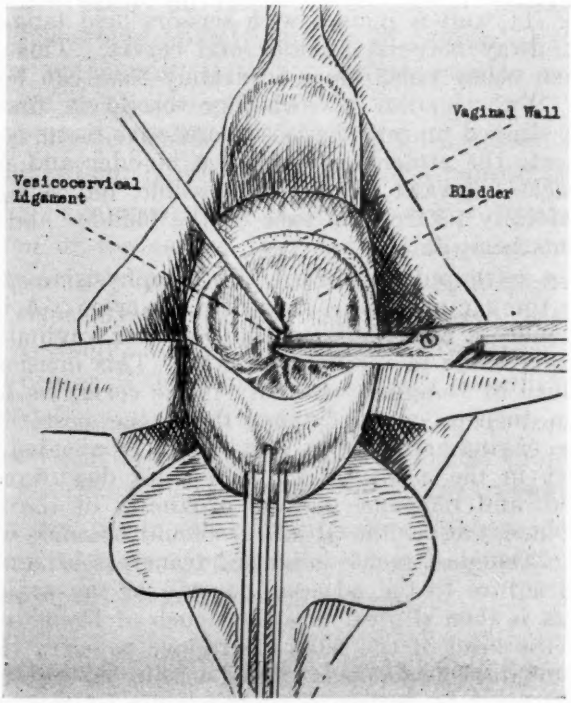


Fig. 1.—The vesicocervical ligament, extending to the cervix from the junction of the floor and posterior wall of the bladder, has been caught with toothed thumb forceps and lifted up to appear as a sagittal fold. This fold is placed on tension by traction on the floor of the bladder toward the symphysis, and is incised with scissors held at right angles to it, midway between bladder and cervix, to open the vesicocervical space.

Carrying the finger higher up the posterior surface of the parametrium, this crushing, ligation, and division of supporting structure is repeated once or twice, depending upon the depth of tissue forming the ligament of Mackenrodt. These ligatures are held long in one forceps. The uterine blood vessels are easily recognized and ligated close to the uterus. This ligature is cut short, so that it cannot be pulled off subsequently. The parametrial supports and vessels on the left side are now ligated and severed from the uterus in the same manner. With each step, the uterus pulls down more readily, exposure improves, and with the main blood supply interrupted, bleeding is negligible.

The uterovesical fold of peritoneum is easily identified and is incised transversely. Its upper edge is secured with one or two sutures held long to prevent its retraction upwards behind the bladder, and the retractor under the bladder is replaced by another inserted into the uterovesical pouch. The fundus uteri is grasped with a single toothed volsellum forceps and "tugged" out through this opening. In some instances this maneuver is facilitated by replacing the cervix in the upper posterior vagina. Depending upon the size of the uterus, it may be necessary to deliver the fundus with successively applied tenacula. In the case of the larger fibroid uterus this is supplemented by cutting out wide deep wedges of tissue held in the tenacula until the fundus

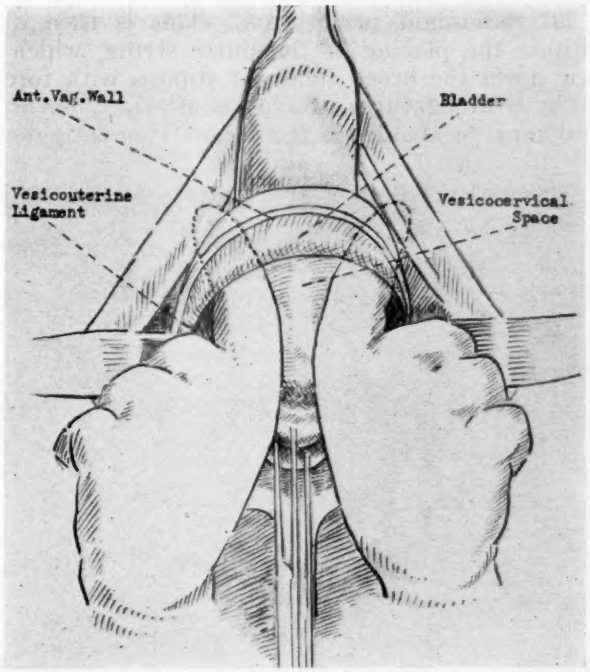


Fig. 2.—The vesicocervical space is entered with the index fingers, and as traction downward is made on the cervix, the bladder is freed from the uterus and broad ligaments, as high and as far laterally as possible. This is done to minimize the possibility of subsequent damage to ureters.

is small enough to deliver. At times one will encounter unforeseen adhesions involving bowel, omentum, or adnexa, but as the uterus is brought more fully into and through the opening, these may usually be dealt with simply. Particular difficulty may be overcome by bisection of the uterus, when the hand can be introduced into the pelvic cavity for further examination and exposure.

When the fundus is delivered (Fig. 3), the upper broad ligaments, including tube, ovarian and round ligaments, are first crushed with forceps as mentioned above, ligated with chromic catgut No. 2, and severed from the uterus, leaving a stump one-fourth of an inch distal to the ligature. The point chosen for ligation will depend upon the degree of prolapse, and the amount of shortening of the structures desired for rebuilding a firm pelvic floor. These ligatures are held long. The remaining portions of broad ligament are ligated and cut away to remove the uterus completely.

The anterior retractor is withdrawn from the uterovesical region of the peritoneal cavity, and replaced between peritoneum and bladder. The posterior retractor is withdrawn from the cul-de-sac and replaced by a short-bladed weighted speculum.

The entire border of the peritoneal opening into the pelvis is now exposed, and just external to it, lying on either side, are the stumps of the uterosacral, lateral cervical, and upper broad ligaments. These upper and lower ligament stumps with intervening endopelvic fascia are next sutured together on either side, so as to make two lateral massive ligamentous supports which will be united later to form the new pelvic floor.

Closure of the peritoneal cavity is effected with a purse-string suture of No. 1 plain catgut, placed just above the free edge of peritoneum inside the broad ligament stumps (Fig. 4). Care is exercised to avoid large blood vessels and ureters by taking shallow bites with the needle. In the presence of an enterocele, the purse-string suture crosses the cul-de-sac at a sufficiently high level to exclude all redundant peritoneum. This is then dissected out and excised. To facilitate the placing of the purse string, which can be difficult, it is safer to draw down the broad ligament stumps with forceps, rather than to pull them down by their ligatures. Inclusion of ovary, omentum, bowel, or the fimbriated tube end, must be avoided as the purse string is tightened.

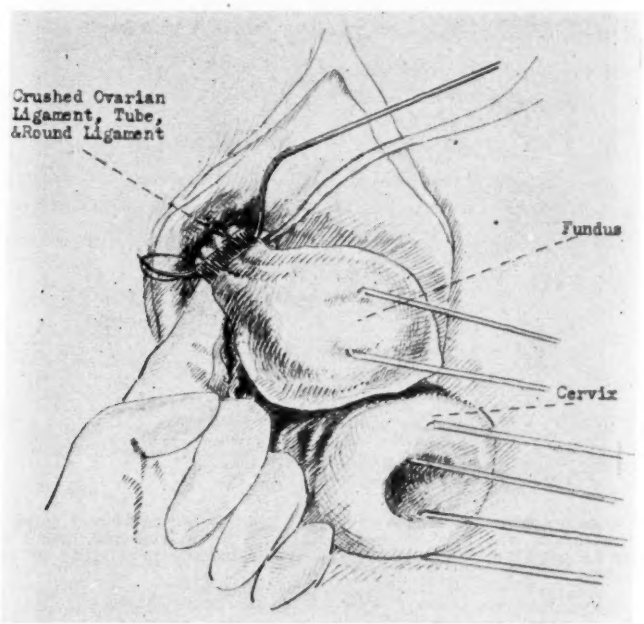


Fig. 3.—The fundus of the uterus has been drawn through the opening in the vesicouterine pouch of peritoneum. The right ovarian ligament, tube, and round ligament have been crushed, and a chromic catgut ligature is being placed to tie off these structures before cutting them away from the uterus. A stump a quarter of an inch long is left distal to the ligature. The remaining broad ligament below these structures is ligated and cut away from the uterus.

Repair of cystocele or urethrocele is now begun by dissection with curved blunt-pointed scissors to free the vaginal mucosa from the underlying fascia. The vaginal wall is divided in the midline to just below the urethra, and flaps raised laterally to expose the redundant bladder. On each side of the urethra, the dissection should be carried to the pubic arch to break down old traumatic adhesions which may interfere with sphincteric function. The strong sub-urethral fascia (cranial portion of the urogenital diaphragm) covering the neck of the bladder is plicated with two or three superimposed mattress type sutures of No. 0 chromic catgut. The importance of this minor procedure in every case cannot be overemphasized, for not uncommonly has the preparation of the anterior wall for repair, without this precaution, caused incontinence in

a previously continent patient. In large cystoceles, the bulging bladder is reduced with a running suture uniting the strong lateral portions of pubocervical fascia.

The upper broad ligament stumps previously made fast to the parametrial and uterosacral stumps are now drawn out and forward with forceps to a position beneath the neck of the bladder. A mattress suture of No. 2 chromic catgut is passed through the subpubic ligament and fascia on the left, deeply through both upper broad ligament stumps to the right subpubic ligament and then back through the stumps to be tied at its point of entry. A second suture in support of this sling is passed from outside the base of the anterior vaginal wall flap on the left, through the subpubic ligament and stumps, and out through the right subpubic ligament and vaginal flap base to be tied later during closure of the anterior wall.

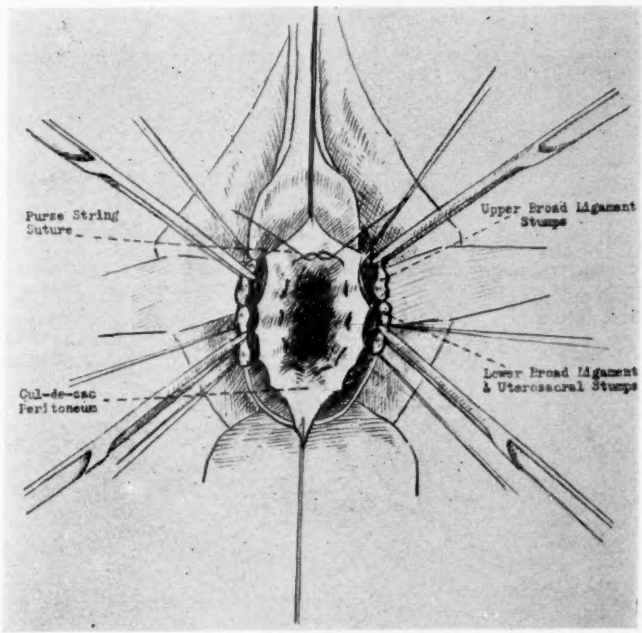


Fig. 4.—Upper and lower broad ligament stumps on each side are shown being drawn outwards and laterally by four forceps, to expose the entire peritoneal opening for insertion of the purse-string suture which will close it. The use of forceps makes it unnecessary to pull the stumps outward by their ligatures which might slip off. If enterocele be present, the purse string passes across the pouch of Douglas at a high level and excess peritoneum below is dissected free and excised.

Upper and lower broad ligament stump ligatures which have been held long are now tied to their fellows on the opposite side to unite the lateral halves of the new pelvic floor.

Excess vaginal flaps are trimmed, and the margins united with interrupted chromic catgut (Fig. 5). Three or four of these sutures are passed deeply through the underlying ligaments which later will contract and pull the vaginal wall up with them. A small gauze drain is left through the suture line near the vault to drain the stump area. It is removed on the fourth postoperative day.

If no enterocele or high rectocele exists, the vault may be closed and the operation completed by a low colporrhaphy and perineorrhaphy. In the presence of enterocele or high rectocele the vault is not yet closed. Incision through the mucosa may be begun where the cul-de-sac was previously entered and may

be extended downward toward the perineum. Usually, however, one incises the perineum transversely, and with blunt scissors dissects free the mucosa from the underlying rectovaginal fascia. In the higher, thinner central portion where the rectum is in closer apposition to the vagina, the mucosa is peeled off by gauze dissection. This should be carried up to the open vault of the vagina and the mucosal flaps raised laterally to expose the stronger lateral fascial regions, and in the lower vagina, the fascial covering of the levator ani muscles.

A crown suture (Fig. 6) is inserted at the vault, uniting the stronger lateral rectovaginal fascial areas and bases of the vaginal mucosal flaps to the uterosacral and lower broad ligament stumps above. The posterior wall fascia is then sutured with interrupted No. 0 chromic catgut (Fig. 7) uniting the fascia near the bases of the vaginal mucosal flaps and in the lower vagina, the sheaths of the levators ani.

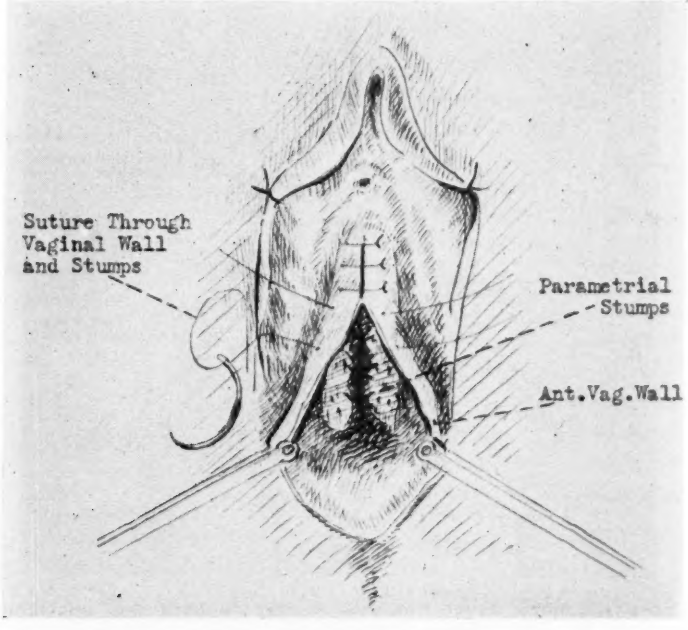


Fig. 5.—All upper and lower broad ligament stump ligatures on the left side have been tied to those on the right and cut short. Vaginal mucosa flaps have been trimmed and the margins are united with interrupted chromic catgut, several of these being passed deeply through the underlying broad ligament stumps. This not only firmly unites the ligamentous supports, but as they retract they will draw the anterior vaginal wall and vaginal vault upward, and increase the length of the vagina. The opening at the vaginal vault is closed excepting for insertion of a small gauze drain, unless high rectocele or enterocele must be dealt with. Then it is left open.

The mucosal flaps are trimmed and their margins united by a continuous stitch of No. 0 chromic catgut picking up small "bites" of the underlying fascia to close "dead space."

The lateral regions of the perineal incision are incised to permit withdrawal of the lower ends of the levator muscles, and these are united with interrupted catgut, the lower stitch picking up anterior fibers of the anal sphincter. The constrictor cunni muscle is restored by a single suture biting deeply into the labia majora. Transverse perineal muscles are united by a running suture of No. 0 chromic catgut which is continued subcuticularly to close the perineum.

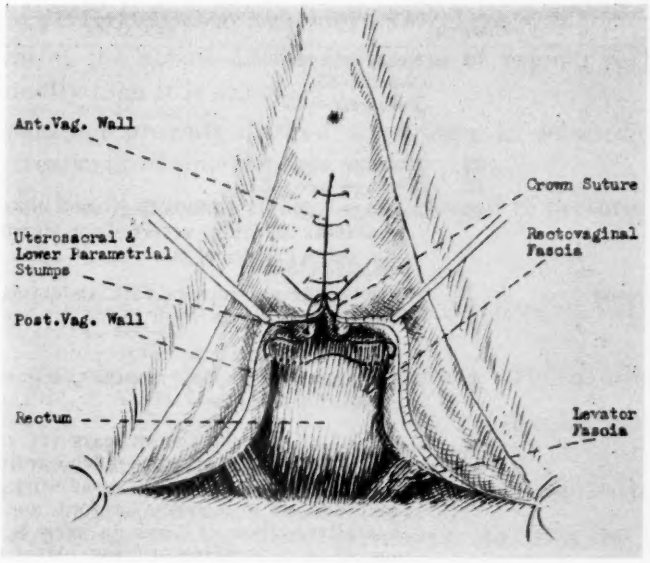


Fig. 6.—This figure shows exposure of the rectovaginal fascia up to the vault of the vagina, and the fascia covering the levator muscles in the lower vagina. In the vault are seen the posterior portions of the uterosacral and lower parametrial stumps. A crown suture of chromic No. 2 catgut has been placed to unite these stumps to the bases of the vaginal mucosa flaps, and the lateral portions of the rectovaginal fascia. This is an important step in the prevention of enterocele recurrence.

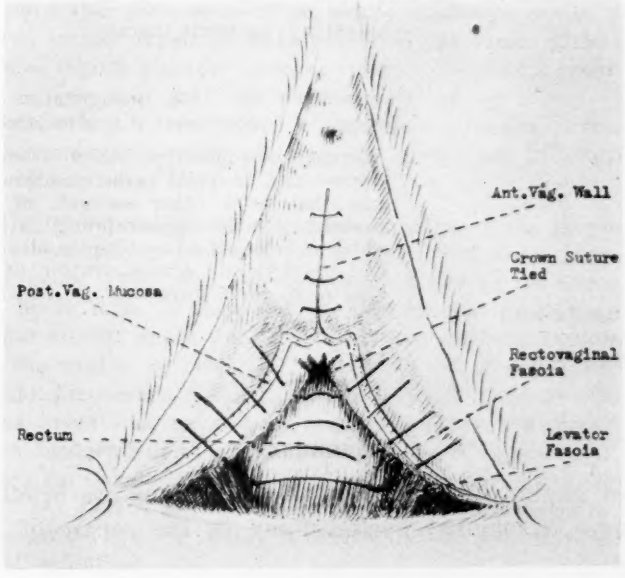


Fig. 7.—The vault of the vagina has been closed by tying the crown suture. A small gauze drain should be shown emerging from the anterior wall just above this point. The rectocele is reduced with interrupted No. 0 chromic catgut sutures, drawing together the bases of the vaginal mucosa flaps and the stronger lateral portions of the rectovaginal fascia. In the lower vagina these sutures include the anterior borders of the levator muscles and their fascial coverings.

TABLE I. CASES, END RESULTS, AND COMPLICATIONS

CASES	NUMBER	REMARKS
Total	77	Average age—50.5 Oldest—85 Youngest—35
Prolapse		
3rd Degree	23	Average age—59.3
2nd Degree	15	Average age—51.4
1st Degree	39	Average age—44.4 including such other indications as abnormal bleeding, severe dysmenorrhea, diseased cervix, large cystocele, etc.
Previous operations	3	Previous vaginal repairs with abdominal fixation of the uterus, and cervix high in vagina, necessitating laparotomy first
Fibroid uterus	13	Five cases of 3 to 3½ months' pregnancy size. Eight cases of lesser size.
Malignancy	3	Ages (a) 46, (b) 64, (c) 69 years Cases (a) and (b) were adenocarcinoma of fundus. Both had postoperative x-radiation therapy. Both well and no recurrence at four and five years postoperative. Case (c) was an early squamous cell cancer of a protruding uterine polyp. No irradiation. Developed recurrence in vaginal vault in 1½ years and died four years after operation
End Results		
Mortality	0	
Recurrence		
Cystocele	0	Size of walnut above a low colporrhaphy. Patient apparently unaware because no complaints
Rectocele	1	
Enterocele	0	At time of reading of paper one case was having nocturnal incontinence only. Since then she has cleared up entirely on estrin therapy
Incontinence	0	
Complications		
Hemorrhage	1	Occurred on the 18th postoperative day from slight slough of upper posterior vaginal wall
Cystitis		A common postoperative complication due to surgical trauma and frequent catheterization. Not more common than with other methods of repair. May be lessened greatly by strapping in a plain catheter, which is released when bladder fills (q 6 to 12 hours) and prophylactic administration of sulfadiazine, grs viiss q.i.d. for 5 days
Ureterovaginal fistula	0	
Vesicovaginal fistula	0	
Rectovaginal fistula	0	
Small vagina	8	Average age 68 years

Summary

1. The most important anatomical considerations are briefly outlined.

2. Advantages of vaginal hysterectomy in the repair of procidentia are discussed.

3. The disadvantages of the operation are considered.

4. A detailed technique of operation is described.

Conclusions

1. The literature on vaginal hysterectomy with vaginal repair to date, mainly lacks detailed description of operative technique.

2. It is felt that this lack of detail may contribute to the fact that the operation is not performed more widely by gynecologists.

3. Removal of the uterus during the course of vaginal repair is indicated far more frequently than it is practiced.

4. The operation presents distinct advantages in selected cases over any other form of treatment of procidentia.

5. Gynecologists in general should be encouraged to perform this operation.

References

Peham, H. V., and Amreich, J.: Operative Gynecology, Philadelphia, 1934, J. B. Lippincott Co., Vol. II, pp. 400-417.
Power, R. M. H.: Surg., Gynec. & Obst. **83**: 296, 1946.
Kennedy, James William, and Campbell, Archibald Donald: Vaginal Hysterectomy, Philadelphia, 1944, F. A. Davis Co., pp. 450-473.
Curtis, A. H.: Obstetrics and Gynecology (G. G. Ward), Philadelphia, 1933, W. B. Saunders Co., Vol. III, pp. 47, 96.
Counsellor, Virgil S.: South. Surg. **5**: 467-478, 1936.
Cherry, Thomas H.: Gynecologic Technic, Philadelphia, 1929, F. A. Davis Co., pp. 141-149.
Emmert, Frederick V.: Surg., Gynec. & Obst. **79**: 281, 1946.
Davis, E. H.: Gynecology and Obstetrics, Hagerstown, Md., 1944, W. F. Prior and Co., Inc., Vol. III, Chap. 18, p. 127.

Discussion

DR. B. P. WATSON, New York, N. Y.—I should like to congratulate Dr. Harrison on one of the best expositions of the anatomy of the essential supports of the pelvic organs and the techniques for their repair that I have ever heard.

I agree with him entirely in his indications for vaginal hysterectomy. After childbearing is over the uterus has no physiological function, and it should be removed if in doing so a better and stronger support to the pelvic diaphragm can be given.

It is essential in any repair to make sure that the vault of the vagina is properly supported, otherwise it may prolapse later, no matter how good a lower pelvic floor repair has been done.

The only detail which I seem to pay a little more attention to than does the speaker is in isolating the supporting fascia of the lower rectum and uniting it in front of any rectocele which may be present.

DR. HARRISON (Closing).—Dr. Campbell mentioned the larger uterus. I would agree that in the presence of various types of pelvic pathology, it would be difficult to peritonealize raw areas. This does not necessarily apply to the fibroid uterus. Quite a few fibroid uteri up to three to three and one-half months' pregnancy size have been removed per vaginam without undue difficulty. This has not been done without some degree of relaxation of the vagina, or prolapse. I would agree, if any operation involved difficulty in closing the peritoneum cleanly. In two or three patients who had had previous Gilliam suspension operations, and whose round ligaments had stretched with prolapse, utilization of these ligaments and peritonealization was not a problem.

I did not say, Dr. Campbell, that I use a running suture in the anterior wall, because I never do. I did say that if the cystocele were of such a size that it required reduction and additional support, a running suture is used to plicate the fascia covering the bladder above the repaired sphincter. The vaginal mucosa is closed with interrupted sutures and some of these should extend deeply to include the underlying ligament stumps.

I have experienced no trouble with estrogen regarding increased friability of tissue. I do not see what would be gained by two or three days' treatment. This, in my opinion, could not improve the circulation and the tone of the tissues sufficiently. I have given small quantities orally over a period of three to four weeks before operation and have not run into the difficulty mentioned.

STERILITY IN THE FEMALE*

KENNETH M. GRANT, B.Sc., M.D., C.M., HALIFAX, NOVA SCOTIA

THE problem of sterility has always assumed considerable importance in the practice of the gynecologist. In fact, there are few problems which test his training, patience, and breadth of knowledge more than that of sterility.[1] No less than 10 to 12 per cent of all marriages are barren. A number of gynecologic lesions may be factors in sterility, yet in recent years much light has been thrown on that large group of cases in which endocrine and physiological factors play an all-important role in its etiology.

The terms sterility and infertility are sometimes incorrectly designated as synonymous. According to Meaker[2] "sterility is the inability to initiate the reproductive process on the part of a couple who have desired and who have attempted to reproduce for a reasonable length of time, ordinarily at least a year." Some suggest three to five years, though less than 10 per cent of initial pregnancies occur after two years. "Infertility" is a term embracing any degree of conceptive capacity below the level of physiologic perfection, or the failure to produce a viable child.

From a clinical viewpoint, sterility in a mating is inability to reproduce, and the fault may be that of either the male or female or both, hence the fertility of a couple must be considered.[3]

Absolute sterility is a condition in which conception is clearly impossible. It is generally due to congenital malformation, such as absence or atrophy of the uterus or gonads, absence of vagina, or to complete occlusion of the Fallopian tubes or ductus deferentes, or when destructive disease has rendered one incapable of fertilization.

Relative sterility is one in which conception may occur, but various factors may make it difficult until existing precluding factors in either mate are corrected. Examples of such include endocrine and metabolic dyscrasias as well as local anatomic defects or lesions.

Acquired sterility is usually considered as the failure of conception after one or more children. It may be due to injuries, operations, new growths, metabolic disturbances, etc.

Selective sterility and fertility are terms used where an individual proves fruitful by one mate but barren by another.

Since the scope of this paper is primarily intended to cover the couple who present themselves seeking a reason for lack of conception, no attempt will be made to cover the subject in minute detail, but rather to outline a reasonably thorough and effective plan of investigation and treatment where indicated.

From the title of this paper one might infer that the female is altogether at fault. Such is certainly not intended, however, as the male partner must bear a considerable portion of fault in the study of childless marriages. Al-

*Presented at the Second Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, Ste. Marguerite, Quebec, Oct. 27-29, 1946.

though some estimate the male to share or accept full responsibility in more than one-half of the cases of childless union,[4] in my own series the incidence was slightly less than 25 per cent. Percentages undoubtedly vary under different social and racial conditions.

In the investigation of sterility in the female, a balanced outlook must be maintained. Laboratory methods, though necessary, should not be depended upon entirely, but incorporated with the results of investigations of the reproductive system in particular and the clinical examination of the patient as a whole.

Parker[5] states, "In order to evaluate the individual case properly the complete cooperation and examination of both partners are essential. The complexity of the problem, at times, and the necessity for repeated examinations must be impressed upon them."

Complete investigation into such a case and its proper treatment may be so complex and distributed over such a wide field as to involve the internist, the gynecologist, the urologist, the endocrinologist, the psychologist, as well as the roentgenologist. Such an inquiry has obvious and practical advantages, such as the elimination, for one thing, of much worthless and harmful treatment of a sort all too prevalent and, in particular, such disasters as operations done for sterility upon the wives of absolutely sterile men. Only if one partner is found to be incurably sterile is it permissible to dispense with the investigation of the other. Also by means of a complete study the most efficient treatment will be effected.[6]

It is obvious, of course, that pregnancy can occur only when the following conditions obtain[7]: (1) Healthy sperm must be deposited at or within the cervical canal. (2) The sperm must be able to ascend without interference and at the proper time to fertilize a healthy ovum. (3) The ovum must implant itself on a suitably prepared endometrium.

Incidence.—Douglas[8] states that 70 per cent of sterile couples show more than one causative factor. In a series of 48 unselected private patients, a single factor was noted in almost 60 per cent of them, and several factors were not commonly encountered.

Investigation.—Gardner[9] states that many factors may contribute to the causation of infertility and that it is necessary to discover and correct as many of these as possible in order to achieve success. The examination should be thorough, can be done efficiently, and much discouragement avoided by adopting a simple but definite plan of investigation and completing it.

The day is fortunately passing, I believe, though repercussions of it are still noted, when a woman complaining of sterility is first advised to have a dilatation and curettage or to have a retroverted uterus corrected by operation, or because of an infantile uterus she is not likely to become pregnant, before a proper inquiry and investigation are carried out, preferably on both partners. Stein[10] says, "the dilatation and curettage are often dispensable, the retroversion often of little consequence, and infantile uterus is usually an inaccurate diagnosis."

The diagnostic inquiry should include the following: (1) A complete medical history preferably of both partners, with special reference to sex history, coital habits, dietary habits, etc., should precede special sterility studies.

One should note particularly the history of acute general infections (scarlet fever), debilitating diseases, nephritis, venereal diseases, appendectomy (especially if patient had drainage), and pelvic operations. (2) A complete physical examination; routine blood and urine tests; evaluation of endocrinological stigmata. (3) A careful examination of the female generative tract, with special reference to the cervix. (4) Examination of the semen. (5) Hühner postcoital test. (6) Tubal patency tests. Hysterograms. (7) Investigation of the endocrine system.

Most, if not all, of the above investigation can be carried out in three office visits or less, depending on the findings. (To obtain the history of a couple, it is usually advisable to consult each one at separate times. In this way premarital incidents are more freely discussed and may be of value in the investigation.)

At her first visit the medical history should incorporate special reference to sexual activity and habits (coital, dietary, etc.), a careful menstrual history, for the menses can usually be considered a fair index of the reproductive development of the patient. Irregularities should be carefully noted and considered as possibly connected with ovarian dysfunction, whereas normal cyclic bleeding, while usually indicating normal function, may occur with anovulatory cycles. Her husband's health should be inquired into, as well as any other factors concerned with sterility, such as difficulties with the sexual act, or the actions of the female partner following intercourse. She is then given a complete physical examination, which should include routine blood tests and serology, urinalysis, and blood pressure. A clinical evaluation should be made of any endocrinologic stigmata from her skeletal configuration, her height, weight, distribution of hair and fat and secondary sex characteristics. Although all of the endocrine glands are more or less intimately related, in fertility it is becoming more apparent that the pituitary is essentially the gland of greatest importance, because of its direct action on the gonads, and indirectly on the thyroid, adrenals, and others.

After the medical examination, the gynecologic examination should follow, and include not only the pelvic but the functional examination as well.

Pelvic examination.—

Special points to be noted are:

1. *Infection in the lower genital tract, including the cervix:* The eradication of vaginal and cervical infections often yields the most gratifying results, and must at least be considered contributory factors in some cases. It may not be easy to explain why such infections as Trichomonas vaginitis and erosion of the cervix produce infertility in some and not in others, but their removal has certainly resulted in pregnancy in not a few of my own cases. This is especially true of erosion of the cervix, the cauterization of which ranks high as a therapeutic measure in sterility. (Caution should be exercised in too deep cauterization and cauterization very soon after the cessation of the menstrual flow to avoid secondary hemorrhage which may be very troublesome.)

The mere probing of the cervical canal by passing a uterine sound (a procedure I now do routinely at the first visit) has given such remarkable results, that in cases where no other gross abnormality exists in the pelvis I advise the patient to curtail further investigation a few months and await results. I feel some of the credit given to the insufflation of patent tubes rightly belongs to the passage of the cannula through the cervical canal.

It need hardly be emphasized that routine smears of the cervix and urethra to exclude gonococcal infection, and examination of Skene's and Bartholin glands should be made.

2. *Structural abnormalities:* In this group would fall those cases of arrested development of vulva, vagina, uterus, adnexa, the absence of one or more, and cases of unruptured or rigid hymen. Hypoplasia of the uterus can usually be suspected when the uterus is about the size of a small walnut, usually anteflexed but may be difficult to outline by palpation (if patient is fat) and when a long, conical cervix with pinhole external os is found. Though hypoplasia of the uterus does not invariably signify sterility, it is a rather common finding in many cases.

3. *Malpositions of the uterus and adnexa:* Retrodisplacement of the uterus has certainly been overemphasized, in the past, as a cause of sterility. However, when associated with a cervix which points toward the anterior vaginal wall, or behind the symphysis and away from the seminal pool, it assumes more importance as a factor. It is well known that many women with such findings readily conceive, and it is no longer common practice to radically correct such displacements. When such a uterus is mobile, it is much less likely to be a cause of infertility than one which is fixed by adhesions resulting from inflammatory disease or endometriosis. The use of a Hodge pessary in such cases, either with or without manual replacement of the uterus, is often successful as a therapeutic measure.

4. *Pelvic inflammatory disease:* Since this is one of the commonest causes of sterility, the adnexa must be completely palpated. It is manifested by the usual signs of tender tuboovarian masses, or indefinite thickening of the bases of the broad ligaments, partial or complete fixation of the uterus, and tenderness on movement of the cervix.

Endometriosis is probably often overlooked as a cause of sterility. I believe it is a rather frequent cause. I can recall several cases in which, on investigation, no known cause could be found for the sterility of the couple, but examination and operation sometime later revealed the presence of a well-established endometriosis. The explanation in early cases is difficult, as the Fallopian tubes are patent, ovulation is rhythmic, yet pregnancy is a rarity. The condition should be suspected when the patient complains of increasing dysmenorrhea which has been acquired during adult life, when the uterus is retroflexed and fixed, when the ovaries are enlarged, tender, and fixed, and when pain is referred to the rectum at the time of ovulation as well as at menstruation.

If a pelvic examination under anesthesia is indicated, as when findings are difficult to evaluate, the time of choice would be just before the onset of the menstrual flow, when an endometrial biopsy can be performed.

There is apparently some disagreement among gynecologists whether uterine fibroids play much part in causing sterility. I feel they are not particularly important unless of such profound size as to distort the cavity of the uterus or cause blockage to the Fallopian tubes. They are more likely to alter the course of a pregnancy rather than preventing its initiation.

Bilateral cystic ovaries, either as a result of hormonal imbalance or new growths certainly play a role in sterility, as pregnancy is a rarity in such cases.

4. *Examination of the semen:* Heckel[11] states that "the final diagnosis of the relative sterility or fertility of a man can be made only by the appraisal of the seminal fluid." If the semen conforms to the normal standards, further examination of the husband is probably not necessary; if not, a physical examination of the husband should be done with special reference to undescended testes, testicular atrophy, and metabolic or endocrine disturbances.

After several days of continence the specimen is preferably collected in a clean and dry glass container, following coitus interruptus, transferred immediately to a clean test tube, corked and placed in sufficiently close proximity to the body to maintain reasonable warmth, and brought to the office or laboratory within an hour. The collection by means of a condom, under similar conditions, in my own experience, does not seem as hazardous to the motility of the sperms as most authorities would have us believe, and I use this method frequently, as less handling is entailed and more constant temperature assured.

The important feature of the examination is the sperm count. Using a white blood counting pipette, diluting 1:20 with 5 per cent sodium bicarbonate solution, counting five blocks of sixteen squares and adding six zeros. An average normal specimen should contain approximately 100,000,000 spermatozoa per c.c., at least 80 to 85 per cent normally formed, and 75 to 90 per cent should exhibit active motility for some hours at room temperature.

The stained smear is also important, and less than 20 per cent should be abnormal.

It would seem wise, therefore, to refer to an interested urologist all husbands whose semen does not conform to those criteria just mentioned.

5. *Hühner postcoital test:* Though the next step usually undertaken is that of determining the patency, or nonpatency, of the Fallopian tubes, the Hühner test is now described as being more in keeping with the preceding paragraph. This is a simple and informative procedure, and requires only a few minutes. It should be performed at the time of ovulation, which is fourteen to fifteen days before the expected onset of the next menstrual period, when the cervical mucus is most receptive to sperms. It is wise to instruct the patient to empty her bladder and rectum before intercourse, and to report for examination within two to three hours following it, without taking a douche.

Samples are aspirated from the vaginal pool and from one, or preferably two levels in the cervical canal and placed on a slide, a cover glass placed over each and immediately examined under the microscope. Within the time allotted

above, if numerous actively motile sperms are seen in both samples, or five to fifteen active sperms present in the mucus from the cervical canal, one can then assume that intercourse has been properly consummated, that sperms are capable of ascending the cervical canal, and that endocervical secretions are receptive to them. Under such conditions one need not feel concerned about the position of the cervix, the length of the vagina, minor abnormalities of the male, such as epispadias, hypospadias, or premature ejaculation. If dead spermatozoa are found in the samples taken from the cervical canal, and active ones found in the vaginal pool, one can properly assume that some hostility exists between the sperms and the endocervical secretions. In such cases, eradication of the endocervicitis undoubtedly present will often result in curing many cases of sterility. I have found such a procedure pays dividends in very many instances. A word of caution is hereby interjected, however, against too extensive cauterization, such as conization, etc., owing to the extensive scar tissue formation which invariably follows such procedures.

6. *Tubal patency and hysterosalpingography:* Tubal insufflation, originally described by Rubin, has probably been the greatest single advance in the diagnosis and treatment of sterility in the female. I have used both carbon dioxide and filtered air, and must frankly state that I have found no difference in the use of either, the patient's reaction depending entirely on the amount insufflated and not on the agent used. I have found the Jarcho Pressometer eminently satisfactory for tubal insufflation.

It need hardly be emphasized that the test should be done within four or five days after the cessation of menstruation. Also that, under normal conditions, the gas passes through the oviducts at a pressure between 60 and 80 mm. of mercury. The rate of increase in pressure should be gradual to avoid spasm of the tubal musculature. The diagnosis of blocked oviducts should not be made definitely until insufflation has failed on three or four occasions, at the same or different sittings. It is probably unwise to carry the pressure beyond 200 mm., though I have seen no ill effects from exceeding this figure on a number of occasions.

Though most authors on the subject insist that the injection of radiopaque substances should be reserved for those cases of apparently stenosed tubes, for purposes of localization, I am quite sure that the use of such substances has a therapeutic value in some cases. Any ill effects from the use of lipiodol or similar oily preparations I have yet to encounter, and within recent years their use has been employed almost routinely in my own practice. The number of cases in whom tubal insufflation failed to bring about the desired results, yet became pregnant following shortly upon the injection of lipiodol, has been rather convincing of its value therapeutically. Also, the information obtained with respect to the location of the block, and the likelihood of success or failure of plastic operations on the tubes supports, to some extent at least, the value of the procedure. The use of supposedly less irritating substances such as Visco-Rayopake of "Roche" has been advocated by various investigators, but I have had no experience with such to date.

In my own practice, in most, though not all cases, choosing the proper time of the cycle, the patient is sent into the hospital for about twenty hours. On the morning following admission a basal metabolic rate is taken. Following this a hypodermic containing $\frac{1}{6}$ grain morphine and $\frac{1}{150}$ to $\frac{1}{200}$ grain scopolamine is given as a sedative and antispasmodic, and an hour later the tubal insufflation and lipiodol injection are carried out. (Methyltestosterone, given orally, in doses of 50 to 100 mg., serves as an excellent antispasmodic, especially when insufflations are carried out in office practice.) It is rarely necessary to use more than 6 or 7 c.c. of oil injected slowly. It is preferable, though not necessary, to watch the instillation through a screen, following which an x-ray is taken. A nonopaque speculum is desirable. Within six to seven hours another plate is taken to determine whether the lipiodol has passed into the peritoneal cavity. If not, the patient is instructed to return in forty-eight hours and another plate taken.

In most cases, where tubes are patent, little or no residue of oil is noted; where the tubes are blocked, it is still plainly visible within them.

The contraindications to the use of tubal insufflation and hysterography are well known and include recent acute or subacute pelvic inflammatory disease, purulent cervical discharge with endocervicitis, infected urethral or Bartholin glands, menstruation or abnormal bleeding, following dilatation and curettage, cardiovascular and pulmonary disease, suspected pregnancy, and severe nervous disorders.

7. *Investigation of the endocrine system:* Gardner says,[12] "Healthy women of childbearing age, who menstruate normally and with some degree of regularity, probably also ovulate fairly regularly. However, individuals without gross genital pathologic changes, who either menstruate infrequently, flow irregularly and scantily, or bleed continuously, probably do not ovulate, such menstrual disorders usually resulting from disturbed function by the glands of internal secretion."

If the investigation so far reveals no obvious cause of sterility, the question of determining whether ovulation is occurring becomes important. Ovulation is difficult to prove. Only presumptive evidence of it may be obtained by endometrial biopsy, taken a few days before the onset of menstruation, or preferably shortly after its onset, to avoid the risk of interrupting an early pregnancy. Ovulation is assumed when the endometrium shows the secretory phase of corpus luteum stimulation. The procedure, however, occasionally is difficult to do, causes not a little pain in nulliparous women especially, and really gives information only for the one cycle reviewed. Recently I have used endometrial biopsy less, and basal body temperature curves more, and have been impressed by its advantages and usefulness. A pronounced biphasic curve is regarded as evidence that ovulation has occurred. At least two cycles must be taken.

Vaginal smears, and determination of the pregnandiol complex between the twentieth and twenty-fourth day are less reliable measures.

The number of cases of hypothyroidism seen in my own practice far exceeds that of any other endocrine problem. Even mild degrees of it are often asso-

ciated with sterility. It is routine procedure with me, in all cases being investigated, to have basal metabolic determinations made, and where variations from the normal spermanalysis exist, to have the husband done also. It is my own feeling that any apparently healthy individual in the minus bracket properly belongs in this hypothyroid group, and that a rate as low as (–7) to (–10), which we have been taught to consider within normal limits, is not so justified. Hypothyroid patients, even of mild degree, respond remarkably well to replacement therapy, and a few dollars' worth of thyroid will often pay dividends far in excess of many times this amount spent for more elaborate forms of therapy and investigation.

Some authorities mention the desirability of blood cholesterol determination, sugar tolerance tests, x-ray of the sella turcica, etc., but I feel they are not often indicated, and rarely offer much help.

Is there a psychologic factor in some cases? We all know of women infertile for years with no obvious reason quickly becoming pregnant following the adoption of a child. I can offer no scientific explanation.

Although it was not intended to discuss treatment in this paper, one should not merely mention endocrine investigation and leave it entirely at that. I am convinced that an appalling amount of time and energy expended in the past ten years or more in the indiscriminate use of sex hormone therapy in cases of sterility sometimes is unwarranted with harmful results.

Endocrine treatment of infertility in the female may be classified as follows: (1) treatment directed at correcting disturbances of endocrine glands which indirectly affect the reproductive processes; (2) treatment directed at correcting disturbances intrinsic in the ovary or uterus.

Siegler[13] states that "in specific treatment the first factor to be considered is whether or not follicle maturation, ovulation, and its sequelae are properly taking place, and therapy should be individualized and cautiously and judiciously applied." He likewise states the necessity of determining which gland or glands are at fault, following which to administer the proper hormone in potent form, in adequate dosage, and over a sufficiently long time. One must remember, however, that excessive therapy eventually results in atrophy of the tissue which produces the hormone administered.

For my own part, except in cases of true genital hypoplasia, and the occasional case of irregular menstrual flow, which thyroid does not correct, female sex hormone is rarely used. In cases, however, where biopsy indicates lack of proper endometrial development, or where pregnandiol assays indicate lowered excretion (i.e., less than 35 mg. in the normal ten to twelve days), large doses of corpus luteum hormone should be tried. Henry[14] apparently found it helpful in selected types of his so-called functionally sterile group. Hamblen[15] covers this aspect of the subject in a masterly way in a recent publication.

Further details of treatment such as plastic operations on blocked tubes in selected cases, or operations on the male to correct aspermia or artificial insemination do not fall within the limits of this presentation.

Summary and Conclusions

The factors most commonly encountered in my own series of cases were more or less in order of frequency: cervical erosions and infections, mild degrees of cerivcal stenosis, hypothyroidism, tubal occlusion, and impaired quality of spermatozoa.

First office visit: A complete medical and gynecologic history is taken, followed by a complete physical examination with special reference to the pelvis. The cervical canal is probed.

A notation of the husband's health, age, habits, etc., are made. Blood serology on both should be done.

Instruction is given her how to take vaginal or rectal temperature. A chart recording this temperature, the menstrual cycle, and dates of coitus is explained and given to her to keep her own record for at least two cycles.

The husband's sperm analysis should be done before the next visit.

Treatment of vaginal discharges of known etiology is advised.

Second visit: If the above records and laboratory reports are satisfactory, a basal metabolic test, tubal insufflation, and, where indicated, uterotubograms are done. If the tubes are patent, she is instructed about the Hühner test.

Third visit: Examination is made of the semen from the vaginal pool and the cervix within one of two hours of coitus, at the expected time of ovulation.

Erosion of the cervix, endocervicitis, etc., are treated when indicated.

The completeness of one's investigation in each case will naturally vary somewhat with the findings. Where absolute sterility is found, further investigation is discontinued.

Our results in overcoming sterility will improve when we are prepared to investigate the infertility of both husband and wife, and not the wife alone. The cooperation of both is necessary.

The survey necessary for the complete investigation of both male and female partners has been presented. Where any abnormality in the male exists, he should be referred to a competent urologist or internist for further study.

The future program may necessitate repetition of doubtful tests.

Six months should be sufficient time to investigate an average case. When all diagnostic data have been correlated, the cause or causes for the sterile mating should be explained to the patients and the prognosis outlined on the basis of established methods of correction and treatment. Where specific treatment is being carried out, a longer time than this may be necessary to justify it. Patients quickly lose interest in their study if they are advised to return in six months or a year, following each bit of investigation carried out.

Physicians, in general, should heed the solicitations of the sterile couple, and, if not interested, should refer them to someone who is. Such patients are usually sincere in their quest, almost always cooperative, extremely grateful when success is achieved, and most deserving of careful investigation and patient study.

References

1. Novak, E.: Text Book of Gynecology, Baltimore, 1944, Williams & Wilkins Co.
2. Meaker, S. R.: Human Sterility, Baltimore, 1934, Williams & Wilkins Co.
3. Siegler, S.: Fertility in Women, Philadelphia, 1944, J. B. Lippincott Co.
4. Gardner, Geo. H.: J. A. M. A. **128**: 245, 1945.
5. Parker, A. S.: The Management of Sterility, Surg. Clin. North America, June, 1945.
6. Meaker, S. R.: Human Sterility, Baltimore, 1934, Williams & Wilkins Co.
7. Page, E. W., and Page, C. W.: Urol. & Cutan. Rev. **48**: 11, 1944.
8. Douglas, G. F.: Abst. Quart. Rev. Obst. & Gynec. **1**: 678, 1943-44.
9. Gardner, Geo. H.: Female Infertility, J. A. M. A. **128**: 295, 1945.
10. Stein, I. F.: M. Clin. North America **27**: 55, 1943.
11. Heckel, M. J.: J. Clin. Endocrinol. **4**: 173, 1944.
12. Gardner, Geo. H.: J. A. M. A. **128**: 245, 1945.
13. Siegler, S.: Fertility in Women, Philadelphia, 1944, J. B. Lippincott Co.
14. Henry, J. S.: Canad. M. A. J. **49**: 167, 1943.

Discussion

DR. MARION HILLIARD, Toronto.—I agree entirely with Dr. Grant's presentation of his investigation, organizing it into three major visits of the patient, one of them being in the hospital. It is difficult to rule out a great many patients who just want to see if they are normal. I have found that 33⅓ per cent of the patients do not return when they find that a complete investigation is necessary both for themselves and their husbands. In my practice I send all the husbands to a urologist who is interested in this type of investigation and treatment.

I have found the use of Hodge pessaries of great value in cases of retroversion of the uterus, and would like to mention that these pessaries are good in cases of acute anteflexion when the cervix is well up in front.

In a discussion of the relative diagnostic values of the Rubin test versus hysterosalpingograms, I have found it possible to put oil through the tube when it was impossible to be sure that air had gone through. Therefore, I would feel that a hysterosalpingogram would be necessary before an absolute diagnosis of sterility could be made. On the other hand, wherever there is any other gynecologic complaint such as intermenstrual discharge, dysmenorrhea, or profuse periods, a dilatation and curettage with the insufflation of tubes will have good therapeutic effect. I use hysterosalpingograms almost entirely and find them very successful. In a series of eighty-four cases, sixteen showed definite abnormalities without any previous histories of any gynecologic complaint or operative interference.

As to the use of thyroid, I agree with Dr. Grant entirely. I put my patients on one grain of thyroid daily, if the basal metabolism rate is not over plus six or seven. There has been some discussion as to whether this may not depress the normal thyroid function, if given over a period of time.

DR. GERIN-LAJOIE, Montreal.—I would like to stress that in our clinic we seldom do an insufflation test. We always use uterosalpingography with lipiodol with better results. We use it not only for sterility but for other diseases where it might be beneficial for the diagnosis. I would like to suggest the removal of the speculum before taking uterosalpingographs as advisable, for there might be findings which would be obscured.

AN IMPROVED OPERATIVE TECHNIQUE FOR SALPINGOSTOMY*

H. W. JOHNSTON, M.D., TORONTO, ONTARIO

(From the Department of Obstetrics and Gynaecology, the University of Toronto, and the Gynaecological Wards of the Toronto General Hospital)

THE operation of salpingostomy whenever tubal occlusion exists is justifiable only when the patient insists on having a child. It is taken for granted that the husband is healthy and fertile. It is also taken for granted that at least two or three previous insufflations have been unsuccessful.

Obstruction in the Fallopian tubes may be present anywhere throughout the lumen. When it occurs at the uterine end, intrauterine tubal implantation is necessary to restore patency. I believe it is the feeling of most gynecologists that this is rarely a justifiable procedure. It does not appear to be surgically or anatomically sound. Salpingostomy, on the other hand, offers possibilities.

Previous to September, 1943, other methods had been attempted by me with no resulting pregnancies. The present technique was suggested when, in the first patient to be reported, a radical operation was about to be begun a few minutes after an unsuccessful insufflation. As the tubes were being handled preparatory to their removal, the striking distention and crepitus suggested a salpingostomy, even if in view of previous experience this operation seemed a forlorn hope.

Since 1943 I have performed salpingostomy three times by this method and, although it seems fantastic, in each case pregnancy followed within a year.

The Operation

The anesthetized patient is placed in the lithotomy position, and one more insufflation is attempted to determine the patency of the tubes. Air is forced into the uterine cavity, and maintained at a pressure of 225 mm. of mercury for two minutes. The intrauterine instrument, if this final test fails, is withdrawn, the patient changed to the Trendelenburg position, and the abdomen opened. Occasionally it is found that the diseased tubes are so irreparably ruined by the previous pathologic process that nothing in the way of a reconstructive operation is possible. However, more often, on palpating the tubes, crepitus will be obtained in one or both, proximal to the "block" which obstructed the distal flow of the air when insufflation was attempted a few minutes before. Even when the tubes are enormously distended as they are in hydrosalpinx, the crepitation is very distinctly palpable to the point of occlusion. At any rate, the practical point is this—that if the tube is incised along its free border at the point of maximum crepitation, a new ostium can be established. When this is performed, a mixture of air and "tubal content" debris gushes forth. As in

*Presented at the Second Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, Ste. Marguerite, Quebec, Oct. 27-29, 1946.

these patients the insufflated tubal wall is thin and avascular usually, the bleeding is slight. This absence of troublesome bleeding is invaluable. For one of the dangers heretofore in salpingostomy was the formation of a hematoma during the fashioning of the new ostium. This, together with the adhesions which usually followed in its wake, invalidated the future success of the operation.

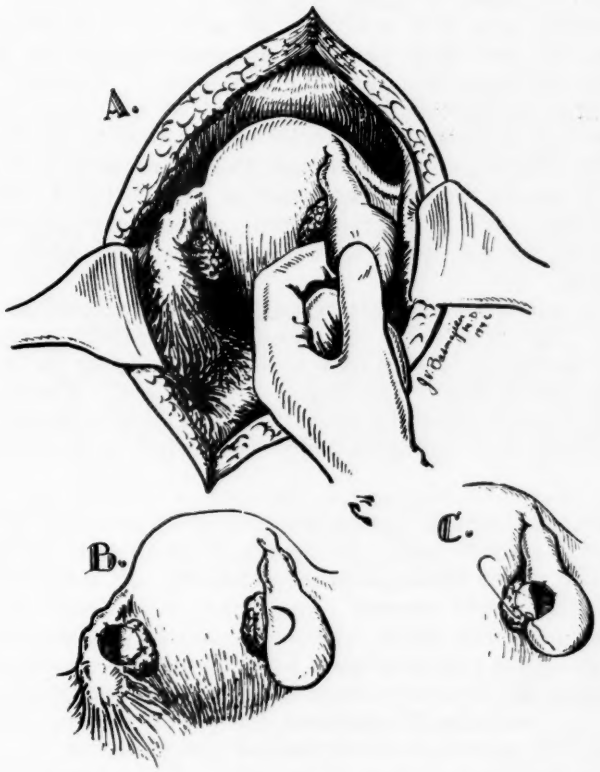


Fig. 1.—*A*, Exploring the abdomen and examining the Fallopian tubes. The tubes are closed. The patient has suffered from pelvic inflammation. The left hand of the surgeon is palpating the right tube. Over the area of maximum crepitation a new ostium will be fashioned.

B, Salpingostomy of the left tube. A curved incision (half-moon) opens the tube. This "trap-door" type of flap leaves a gaping wound, and there is very little chance of the ostium closing. The blood supply to the flap is preserved so that sloughing will not occur. By suturing it down to the ovarian hilum (which is practically avascular) every opportunity is given the ovum to tumble into the gaping mouth of the artificial ostium. The curved line on the right tube delineates the site of the incision.

C, Salpingostomy of the right tube. The flap is being sutured to the hilum of the ovary with fine chromic surgical gut on a small atraumatic needle.

The fashioning of the ostium may be left to the ingenuity of the surgeon. Fine silk or fine surgical gut on an atraumatic needle is advised. Any unnecessary separation of adhesions is to be avoided. Adhesions tend to reform. If it is possible to establish the artificial opening near the ovary, this should be done, but it should be remembered that the adnexa resent rough handling, and show their resentment in the form of troublesome oozing. As mentioned above, this may defeat the purpose of the operation. Nor is it necessary in this procedure to test the patency of the tubes from above by attempting to pass air, fluids,

probes, bristles, etc., into the uterine cavity. These procedures, involving as they do needless intratubal trauma are to be condemned. The gush of air when the scalpel opens the lumen is ample proof that the tube is patent, as far as the site selected for salpingostomy (See Fig. 1, *A*, *B*, and *C*).

Case Reports

CASE 1.—*Mrs. W.*, aged 28 years, was seen on Sept. 4, 1943. At 19 years of age she had married, and gave a history of pelvic inflammation following the mating. During the past four years, numerous attempts at insufflation were negative, and she had been told that her tubes were "blocked." On Sept. 17, 1943, a final testing was carried out. The pressure was raised to 225 mm. and kept constant for two minutes. The tubes were found to be closed. The abdomen was opened. The right tube showed the characteristic ravages of pelvic inflammation, and was in the quiescent state of hydrosalpinx. It was impossible to find any semblance of a natural ostium. A new one was fashioned over a suitable spot where the adhesions were least dense, and where crepitation was most easily elicited.

The left tube appeared edematous, and air had traveled along its lumen to its middle third. The outer third was bound down tightly to the sigmoid colon. A salpingostomy was done on this tube by slitting it along its free border at the spot of maximum crepitation. The abdomen was closed. The convalescence was uneventful. Ten months after the operation I received a letter from her physician stating that she had unfortunately miscarried in the midtrimester of a pregnancy.

CASE 2.—*Mrs. G.*, aged 28 years, was seen on June 12, 1944. This patient had been married for four years. A history of painful menorrhagia antedated her marriage. The pelvic findings were as follows. A retroverted, large, fixed uterus, with small bilateral masses. The cervix was clean. A tentative diagnosis of endometriosis was made. Previous tubal insufflations had been pronounced negative. Under anesthesia, a final testing was done. The tubes were closed. On opening the abdomen the diagnosis of endometriosis was confirmed. The right tube was occluded throughout the whole lumen, at least, there was no proof of air having passed as no crepitation was obtained.

The left tube and ovary were "dug out" of the pouch of Douglas. The tube was engorged with air as far as its distal third, and the fimbriated end was densely adherent to the ovary. A new ostium was fashioned over the free border of this tube at the point of maximum crepitation. The uterus was then suspended and the appendix removed. The convalescence was uneventful. The following year she conceived, and unfortunately miscarried. On Oct. 5, 1946, Dr. Adamson of Hamilton delivered her of a living female child.

CASE 3.—*Mrs. M.*, aged 25 years, was seen on Sept. 3, 1944. This patient had been married for five years. Previously she had been operated upon by a general surgeon for pelvic inflammation, and the appendix, the right ovary, and part of the right tube removed. The menses were regular and painless. On Oct. 21, 1944, a routine insufflation of the tubes was done. and it was found that the air at a steady pressure of 225 mm. of mercury failed to pass into the peritoneal cavity. The abdomen was then opened. The remaining part of the right tube was very distended, and "crackled" on palpation. It was about three-fourths inch long, and clothed with dense adhesions. After freeing the minimum of adhesions necessary to make the plastic change feasible, a curved half-moon incision was made over the free border and this was deepened until air and tubal debris oozed forth. A new orifice was fashioned using interrupted sutures of fine chromic surgical gut on an atraumatic needle.

The left tube was now examined and found to be a typical hydrosalpinx with a closed fimbriated end. It had become enormously distended with air as a result of the attempted insufflation. The closed tube was separated from the outer pole of the ovary, and salpingostomy was performed simply by removing the distal part by circular amputation. On Dec. 20, 1945 (thirteen months after the operation), I delivered this woman of a living male child weighing 8 pounds 3 ounces.

Summary

Salpingostomy is justifiable in certain cases. It is admitted that the operation has a limited field of usefulness. A technique is described in which preparatory to laparotomy, air is forced into the uterus at a high pressure, and salpingostomy is then performed on the tube over the area of maximum crepitation.

Only three cases are reported, but the successful results seem to indicate the value of the method.

Discussion

DR. VAN WYCK, Toronto, Canada.—A review of the subject of plastic operations on the tube for the cure of sterility has not given a very favorable picture. The reason is threefold. The relatively few live babies achieved by these methods; the undue proportion of ectopic gestations resulting; and finally the complications which may from time to time follow any laparotomy.

Dr. Johnston has described a modification of technique in which he has utilized tubal insufflation: (1) To determine the point of obstruction. (2) To select the best operative site for fashioning a tubal ostium. The maintenance of the distention of the tube when the abdomen is opened, renders the operative site more avascular and the operation more practicable.

One cannot, in such a small series, draw many conclusions. One cannot, also, neglect the fortuitous. However, I should like to suggest one procedure which might be added to his method. The preliminary lipiodol salpingography might still further eliminate those cases where plastic operation might give no reasonable hope of success.

A STUDY OF BREECH DELIVERY*

ALBERT E. TRITES, M.D., VANCOUVER, B. C.

(From The Vancouver General Hospital)

THE serious infant mortality associated with breech presentation is emphasized in all standard texts of obstetrics, the total uncorrected fetal death rate being placed at about 20 per cent. Stander states that approximately one-third of this loss is directly due to the presentation itself, while Holmes and Evans give the mortality for the child as 10 per cent. As suggested by Tompkins and others, it seems likely that the fetal risk has been exaggerated in the minds of obstetricians by the failure to distinguish between the infantile death rate associated with breech presentation and the mortality of breech delivery per se. The fact that the presentation is frequently associated with prematurity, placenta previa and fetal abnormalities must be borne in mind; all conditions carrying an inherent serious risk to the child.

Furthermore, statistics on breech delivery as published from large clinics are undoubtedly influenced by the fact that a considerable percentage of deliveries by interns in training is included.

Recent studies to determine the intrinsic risk of breech delivery present a more cheerful view of the picture. Hansen has collected a series of 112 consecutive cases from private practice with a corrected fetal mortality rate of 0.8 per cent. External version was not practiced, and the conduct of labor and delivery was most conservative. Tompkins has presented a series of 211 breech cases delivered by a group of 17 obstetricians in Philadelphia, all diplomates of the American Board of Obstetrics and Gynecology, with a corrected mortality rate of only 2.7 per cent. Perhaps the most striking results are those of Greig, who reports sixty personally delivered cases of breech presentation in primigravidas with but one stillbirth and no neonatal deaths. His method of delivery is extremely conservative, spontaneous birth with a minimum of manual assistance being the rule. Local (pudendal block) anesthesia was used, his recent cases having received no general anesthetic even for delivery of the head. Greig believes that fully 90 per cent of breech deliveries in primiparas can be spontaneous.

While admittedly these excellent results are reported by skilled obstetricians, it should be noted that in the conservative management, as recommended by Hansen and Greig, success depends more upon method than on manual dexterity, and that a similar technique therefore may be followed with considerable assurance, even by the neophyte in obstetrics.

*Presented at the Second Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, Ste. Marguerite, Quebec, Oct. 27-29, 1946.

When we consider the effect of a more radical policy of delivery, namely elective breech extraction upon complete dilatation of the cervix, the fetal results are not comparable. Even in expert hands, the procedure is associated with a reported mortality for the child of from 6 to 10 per cent, although Goethals did succeed in achieving a mortality rate of 2.3 per cent in one series. Obviously, should the practice of elective extraction become widely adopted, the loss would be much greater. In an analysis of over 3,000 breech deliveries in the borough of Brooklyn, Gordon showed a fetal death rate of 18.7 per cent following extraction.

Material

A personal series of sixty consecutive cases of primary breech presentation, fifty-five of which were delivered vaginally, is presented as a further evidence of the benefits of a conservative policy in management. There were thirty-seven primiparas in the latter group. Since the purpose of the study was to determine the essential hazard to the child solely as a result of breech delivery, it does not include premature babies of less than 2,500 Gm. in weight. As emphasized by Beck and Philpott, the risk to premature infants in breech delivery is considerable because of the relative disparity in the diameters of the body and head. However, since maternal toxemia, atalectasis, and other conditions incident to prematurity may be associated, it is often difficult to determine exactly the deciding factor in the fetal mortality. Twin babies were excluded, since the second twin, when presenting by the breech, has its passageway already prepared. Gross monstrosities incompatible with continuing fetal life are excluded. Otherwise, the group represents the writer's total experience with breech delivery in private practice extending over a period of ten years. Cases of internal podalic version and extraction not being primary breech presentations are omitted. It has been the general policy (especially in the earlier years of practice) to make at least one attempt at external version when a breech was discovered during antenatal examination, otherwise this small series would have been considerably larger. In a few instances, however, the discovery of the presentation came as a surprise when the mother was seen in early labor. As it stands, the series reflects the experience of an average obstetrician in private practice following a definite plan of noninterference in labor in so far as possible. That an element of good fortune may have been associated with the results is freely admitted, and it is quite possible that a larger experience may show a higher fetal mortality rate.

Because of its small size, the personal study is supplemented by a similar review of the uncomplicated breech deliveries occurring consecutively in the Vancouver General Hospital from Jan. 1, 1945, to June 30, 1946, inclusive.

TABLE I. INCIDENCE OF BREECH CASES AT VANCOUVER GENERAL HOSPITAL
(JAN. 1, 1945, TO JULY 1, 1946)

1. Viable births	5987
2. Total breech cases	224 or 3.8%
3. Uncomplicated breech deliveries	145 or 2.6%
(Twins, monstrosities, less than 2,500 Gm. excluded)	

While many of the cases in the latter series were delivered by specialist members of the attending staff, fully 60 per cent of them were under the care of various general practitioners of the visiting staff or were delivered by interns in training. The over-all group is, I believe, sufficiently large to indicate the general character of the fetal results in breech delivery at the Vancouver General Hospital.

The outcome for the child in the two series is shown in Table II.

TABLE II. FETAL RESULTS IN BREECH DELIVERY. VANCOUVER GENERAL HOSPITAL GROUP (JAN. 1, 1945, TO JULY 1, 1946)

NUMBER	STILLBIRTHS	NEONATAL DEATHS	FETAL MORTALITY
145	7	1	5.5%
	Personal Group (1935 Onward)		
55	1	1 (Congenital heart)	3.6%
		Corrected	1.8%

(Premature babies of less than 2,500 Gm., twins, and gross monstrosities excluded)

There was no maternal mortality in the entire series.

The Management of the Patient

Granting the conclusion that fetal mortality is largely dependent upon the success or failure to achieve a spontaneous or nearly spontaneous delivery of the breech, the conduct of labor is directed to this end throughout. The procedure as described is chiefly applicable to delivery in primiparas, and is modified as necessary in multiparas.

To avoid unnecessary worry, the expectant mother with a breech presentation need not be informed of the fact before labor commences. If she is aware of it, the importance of the condition is not emphasized. However, when labor is established, it is well to acquaint her of the situation, and to enlist her aid for the delivery to come. One explains that since her active cooperation in the birth will be required, she will not receive deep analgesia or amnesia. To this end such drugs as paraldehyde, scopolamine, and the barbiturates in high dosage, which tend to cloud the sensorium and produce restlessness, are contraindicated. However, since uterine inertia is not uncommon, the patient is protected against exhaustion and dehydration by adequate sedation and fluid administration.

TABLE III. DETAILS OF PERSONAL SERIES

A. *Number of Cases*	60	
Primiparas		42
Multiparas		18
Average age of Primiparas		27
B. *Type of Delivery*		
1. Spontaneous with manual aid		43
2. Extraction		12
3. Cesarean section		5
4. Forceps to aftercoming head		18

When the cervix is believed to be fully dilated, the patient is prepared as for delivery, and a vaginal examination made to rule out the possibility of a prolapsed cord and to satisfy oneself that there is no remaining rim of the cervix. Not infrequently, and especially in footling presentations, the leading part may be visible at the vulva before cervical dilatation is complete. Premature expulsive efforts in such instances may result in the cervical rim offering obstruction to the aftercoming head. Sufficient time should be allowed to ensure that the cervix is not only completely dilated, but also "paralysed," as someone has aptly expressed it.

TABLE IV. DETAILS OF PERSONAL SERIES

C. *Average Duration of Labor*	
Primiparas	20 hours
Multiparas	6 hours
D. *Average Weight of Child*	
For Primiparas	3,342 Gm.
For Multiparas	3,516 Gm.
E. *Greatest Weight of Child*	
For Primiparas	4,290 Gm.
For Multiparas	4,050 Gm.

TABLE V. PERSONAL BREECH CASES DELIVERED BY CESAREAN SECTION

NO.	AGE	PARA	PELVIS	X-RAY	TRIAL LABOR	WEIGHT OF CHILD	REMARKS
1.	25	$\overline{0}$	Android	Yes	None	3,010 Gm.	Marked contraction of midpelvis
2.	27	$\overline{0}$	Gen. contracted	Yes	None	3,150 Gm.	
3.	27	$\overline{0}$	Android	Yes	None	3,460 Gm.	Very small outlet
4.	32	$\overline{0}$	Android	Yes	None	2,965 Gm.	Small mid-pelvis
5.	33	$\overline{0}$	Normal	Yes	24 hours	3,655 Gm.	Cervical dystocia

Careful and frequent auscultation of the fetal heart is practiced throughout the second stage of labor so that an immediate extraction may be undertaken should fetal distress appear. If this precaution is observed, the stage of expulsion may be extended beyond the traditional two or two and one-half hours without anxiety if progress is being made. A too prolonged second stage, however, may favor the development of a contraction ring. The practice of "breaking up the breech" by bringing down a foot by Pinard's maneuver was rarely followed, it being considered preferable to perform complete extraction under full anesthesia if failure of advance occurred in the second stage of labor with the breech high.

When the perineum becomes distended, a pudendal nerve block anesthesia is induced using 1 per cent procaine solution containing three minims of epinephrine to the ounce. In a few minutes the pelvic floor may be painlessly dilated, if desired, by the familiar "ironing-out" maneuver. A wide episiotomy is then made, following which descent and delivery of the breech usually occur promptly. After the birth of the umbilicus, complete general anesthesia is induced and the anesthetic agent must act rapidly. A slowly acting anesthetic such as ether may be worse than none. As the anterior scapula presents, it is pushed toward the fetal spine as recommended by Potter, thus delivering the anterior arm. Should the anterior shoulder not appear promptly or the anterior arm be extended, the child's body is drawn slightly downward and rotated so as to make the posterior shoulder become anterior by the method so well described by Lövsett, though probably practised by obstetricians for many years. The rotation is then reversed to deliver the other arm. One trial is made to deliver the head by the modified Wigand-Martin maneuver. If easy delivery is not forthcoming, forceps are promptly applied. Whatever method is employed for the delivery of the head, flexion by jaw traction with rotation under the pubic arch is maintained so as to roll the head slowly out of the pelvis. General anesthesia is discontinued with the birth of the head, and the episiotomy repaired at leisure while the local anesthesia is still effective.

In guiding the head through the pelvis the widest available diameters as determined by x-ray pelvimetry should be considered. I have had no experience with the Burns-Marshall technique of allowing the child to hang by the head so as to draw it into the pelvic cavity, but its enthusiastic recommendation by British obstetricians would suggest its use when necessary.

In delivery of the shoulders, arms, or head, I am convinced that it is a mistake to adhere rigidly to a planned routine in the face of an apparently conflicting mechanism. One must adapt the procedure according to circumstance.

Discussion

Many talks with younger practitioners on the subject of breech presentation has led one to the conclusion that there exists a considerable fear of the "breech birth" in the mind of the profession at large based upon the serious prognosis for the child. This exaggerated dread may express itself by too strenuous attempts at external version, by excessive haste or roughness in delivery, or by a frequent recourse to cesarean section.

The merits of external version when gently performed have been repeatedly attested, and it is far from my intention to question its value. Nevertheless, it is often most difficult of accomplishment, in the very instances where it would be highly desirable, namely, in primiparas where not infrequently a tense abdominal wall or engagement of the breech may prevent its performance. It would seem that the hazard of breech delivery is not sufficiently great to justify too vigorous or persistent attempts at external version in difficult instances, nor in particular to warrant its employment under anesthesia. An increasing number of cases of placental separation and other accidents are being reported.

The pharmacologic method of version during pregnancy by means of purgation as recommended by certain Spanish-American obstetricians is interesting and harmless and deserves more widespread clinical trial.

When we consider cesarean section, it is apparent that abdominal delivery must have wider application in breech presentation than in vertex cases. Since disproportion may not become evident until the aftercoming head reaches the midpelvis, trial labor is of little value. There is, moreover, no time for head molding. Careful clinical and radiologic examination of the maternal pelvis should generally indicate the way to safety. Even with the normal pelvis, the hazard to the overlarge child (of more than 4,000 Gm.) is to be remembered, especially in elderly primiparas. However, breech presentation as such should not be considered an indication for cesarean section except when the pelvis is contracted or under other unusual circumstances.

In this connection it is well to re-evaluate the slow labor in primiparas after a test of from twelve to eighteen hours. Ineffectual uterine contractions with a prolonged and that the risk to the child will be increased proportionately. thick, slowly dilating cervix will generally indicate that the labor will be unduly Delivery by cesarean section may be the best solution in some of these cases.

Summary and Conclusions

Belief is expressed that a more favorable fetal mortality rate than generally quoted is possible, based upon the following considerations:

1. A complete study of the maternal pelvis by clinical and radiologic methods with delivery by cesarean section if the pelvis is contracted.

2. A conduct of labor designed to achieve a high incidence of spontaneous delivery of the breech with interference only on definite indication.

3. Constant personal supervision of the second stage of labor by the attending obstetrician.

4. The utilisation of local anesthesia, wide episiotomy, and frequent application of aftercoming head forceps in delivery.

References

1. Beck, A. C.: Am. J. Obst. & Gynec. 51: 173, 1946.
2. Burns, J. W.: J. Obst. & Gynaec. Brit. Emp. 41: 923, 1934.
3. Dieckmann, W. J.: Am. J. Obst. & Gynec. 51: 349, 1946.
4. Goethals, T. R.: Surg., Gynec. & Obst. 70: 620, 1940.
5. Gordon, C. A., Garlick, R., and Oginz, P.: Am. J. Obst. & Gynec. 28: 140, 1934.
6. Greig, D. S.: J. Obst. & Gynaec. Brit. Emp. 52: 122, 1945.
7. Hansen, E. M.: Am. J. Obst. & Gynec. 41: 575, 1941.
8. Holmes, R., and Evans, C. B. S.: Gynecology and Obstetrics (Davis)—Vol. 1. Chap. XVII, Hagerstown, Md., 1944, W. F. Prior Co., Inc.
9. Lovsett, J.: J. Obst. & Gynaec. Brit. Emp. 44: 696, 1937.
10. Marshall, C. McI.: J. Obst. & Gynaec. Brit. Emp. 41: 930, 1934.
11. Odell, L. D.: Am. J. Obst. & Gynec. 46: 722, 1943.
12. Philpott, N. W.: Canad. M. A. J. 41: 468, 1939.
13. Potter, I. W.: The Place of Version in Obstetrics, St. Louis, 1922, The C. V. Mosby Co.
14. Potter, M., Erving, H., and Brown, J.: Am. J. Obst. & Gynec. 49: 567, 1945.
15. Stander, H. J.: Textbook of Obstetrics, New York, 1945, D. Appleton-Century Co.
16. Tompkins, P.: Am. J. Obst. & Gynec. 46: 695, 1943.
17. Walsh, J., and Kuder, K.: Am. J. Obst. & Gynec. 47: 541, 1941.
18. Waters, E. G.: Am. J. Obst. & Gynec. 43: 715, 1942.

Discussion

DR. ROSS MITCHELL.—In his well-reasoned paper Dr. Trites shows that the prevalent gloom in breech presentation is unjustified, and that the risk to the fetus in primary breech presentations can be much less than is usually stated. Probably it is no greater, and may be even less than for occiput posterior positions. Personally, the latter have given greater worry than breech presentations.

The bugbear of disproportion can be obviated by careful clinical observation, supplemented when necessary with x-ray examination. The incidence of cesarean section need not be high. Dr. Trites presents from his own practice sixty consecutive cases of primary breech presentation with five abdominal deliveries. In my own practice from July 1, 1936, to the present date there were fifty-six cases of primary breech presentations at term or near term with two abdominal deliveries. The combined groups may be presented thus:

Method of Delivery

Vaginal deliveries 109	Cesareans 7	Total 116

Vaginal Deliveries

Primiparas 73	Multiparas 36	Total 109

Fetal Mortality in Vaginal Delivery

Total 109 Stillbirths, 1 Neonatal Death,* 1 fetal mortality, 1.72%

In my own series of fifty-four deliveries there were four babies weighing 9 pounds 11 ounces; 9 pounds 10 ounces; 9 pounds 3 ounces; and 9 pounds 2 ounces, respectively, and a total of eight weighing 8½ pounds (3,800 Gm.) or over. The management of delivery was substantially that advocated by Dr. Trites. I can emphasize the value of local anesthesia, of deep episiotomy and of not hurrying the head through the birth canal.

*(Congenital heart) Corrected mortality 0.86 per cent.

In his management Dr. Trites is conservative. The mother's forces are utilized to the full, and he interferes only when there is failure of progress. This wise restraint is the more admirable in that it calls for a minimum of general anesthesia and for no unusual dexterity on the part of the operator.

DR. WM. A. SCOTT, Toronto.—I do not use spinal anesthesia as a routine in obstetrics, but have adopted it to a greater extent than in the past. I use a low spinal anesthesia in all breech deliveries at or near term, and also when I anticipate a difficult operative delivery in a vertex presentation. The anesthetic need not extend to any great height, and it gives a relaxation of the soft tissues that facilitates all operative procedure.

I should like to ask Dr. Trites just what advantages a local, supplemented by a general anesthetic has over a low spinal anesthesia.

Dr. Trites laid down the dictum that a careful radiologic study of the pelvis would determine those cases where, because of pelvic disproportion a cesarean section is indicated. I would like his opinion on a somewhat controversial point. In an elderly primipara in whom there is no disproportion, with a breech presentation and extended legs, one anticipates a difficult delivery. Under such circumstances is one not justified in doing a cesarean section in the interests of the child?

DR. B. P. WATSON, New York.—We have for many years at the Sloane Hospital carried out a very conservative policy in breech delivery. Our teaching has been that practically every breech should deliver spontaneously. Full dilatation of the cervix and stretching of the pelvic floor is allowed to occur by the breech itself. The frank breech is not broken up unless descent is arrested.

The greatest aid in reducing fetal mortality is episiotomy. This should be done as soon as the breech begins to stretch the perineum. It should not be deferred until after the breech has been born and difficulty with the aftercoming head is encountered. When we follow these rules we do not fear a breech delivery anymore than we do a vertex.

DR. TRITES (Closing).—It was gratifying to note that Dr. Mitchell shares my feelings with respect to breech presentation, and I should like to congratulate him on his results. I have had no experience with the use of the Voorhees' bag in breech cases, but I believe that it might have a place when the cervix was dilated to 4 or 5 cm. and progress slow. Here it might be used to advantage.

In replying to Dr. Scott, I have had no experience with spinal anesthesia in delivery, but am assured that it gives excellent relaxation of the pelvic floor, and I believe it might be of special use in certain cases. The particular advantage of local anesthesia is that the patient may use her voluntary powers up to the time of actual delivery. There is also the question of the availability of trained anesthetists, which was until recently a constant difficulty in the hospital where I work. Dr. Scott mentioned the question of elective cesarean section in the elderly primipara with a frank breech presentation and a normal pelvis. It is quite true that the risk to the child may be increased because of the patient's age. In deciding on the method for delivery, I would be guided by two or three factors—first, the estimated size of the child, and secondly the condition of the cervix. If the cervix were soft and well effaced when labor commenced, the child not obviously overlarge, and the breech well engaged, I would give such a patient a test of labor to judge her progress with the thought that I could change my method of delivery at the end of twelve hours, if considered advisable.

Replying to Dr. Grant, his question is well taken regarding the necessity of "ironing-out" the perineum before delivery. One of the advantages of local anesthesia is that the pelvic floor will be relaxed, and in the average patient there will not be much need to do any ironing-out; although, at times it is helpful to do so when the patient has a rigid levator ani muscle.

I am grateful to Dr. Watson for his support of the conservative method of treatment, and agree fully that episiotomy should be done early, well in advance of the birth of the breech.

OVARIAN PREGNANCY*

R. T. Weaver, M.B., D. L. Adamson, M.D., and F. L. Johnson, M.D.,
Hamilton, Ontario

(From the Department of Obstetrics and Gynaecology, Hamilton General Hospital)

Mrs. I. M., a 42-year-old white female, entered the Hamilton General Hospital Sept. 17, 1945. At that time she complained of "no periods for twelve months."

Her last normal menstrual period was Sept. 1, 1944. She had slight nausea with occasional vomiting in October, 1944, which only lasted for approximately two weeks. She visited her doctor in November, 1944, at which time a diagnosis of pregnancy was made. She did not return as she felt perfectly well. She was never aware of any abdominal enlargement or pressure of abdominal mass, nor did she feel any fetal movements. She continued well until April, 1945, when she began to have pains around the level of the umbilicus accompanied by marked constipation, and "a lot of gas." This lasted for approximately one week, during which time she was very tired.

From the middle of May to the middle of June, 1945, she had intermittent spotting of blood from the vagina accompanied by small clots which lasted five days. There was no bleeding since that time. She had intermittent pain in the right lower quadrant for two weeks, which would disappear with rest.

In August, 1945, she was examined regarding accepting steady employment. At this time she was referred for x-ray examination of the abdomen. The report was as follows:

A film of the abdomen showed the presence of a single fetus of approximately five months. The midpoint of the head was at the level of the posterior iliac crest on the right side. There was overriding of the fetal skull bones, breech presenting, spine to the left. No placenta could be identified with any certainly as such, and the total mass was rather smaller than one would anticipate in consideration of the various elements contained in a pregnant uterus. No abdominal masses other than this pregnancy were identified.

Hospitalization was advised but she did not report for another month.

She had two previous normal pregnancies and deliveries twenty-four and twenty-two years ago.

No abnormalities were present until the onset of her present illness.

Physical examination on admission showed her blood pressure to be 124/82; temperature 98.2° F.; pulse 70; respiration 18; red blood cells, 5,400,000; white blood cells 8,000; hemoglobin 97 per cent.

Urinalysis and blood chemistry normal.

Examination essentially normal except for abdomen and pelvis.

There was a firm mass, size of football, rising from pelvis to just above level of umbilicus lying more to the right than to the left side. There was no tenderness, and the mass seemed partially moveable. The cervix was firm, elongated, and closed. It was thought that the uterus could be palpated in the cul-de-sac, and this mass was probably extrauterine.

*Presented at the Second Annual Meeting of the Society of Obstetricians and Gynecologists of Canada, Ste. Marguerite, Quebec, Oct. 27-29, 1946.

A laparotomy was performed and the mass was found to be situated in the location of the right ovary and obviously containing the pregnancy. The omentum and small bowel were adherent to the mass. After freeing of adhesions the mass was seen connected to the uterus by the ovarian ligament, which was enlarged. The uterus was slightly enlarged, and retrodisplaced in the cul-de-sac. Both tubes were lying free and looked normal. The left ovary was cystic, about the size of a lemon, lying free in the left fossa. The right ovary containing the

Fig. 1.—Specimen opened showing surrounding capsule of ovarian tissue.

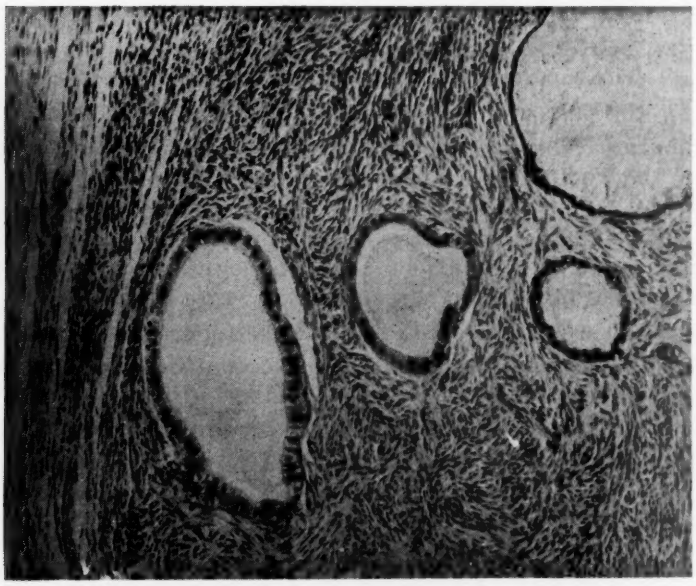


Fig. 2.—Section of capsule showing ovarian tissue and gland suggestive of endometrial glands.

pregnancy and the left ovary containing the cyst were removed. The postoperative course was uneventful, and she was discharged on the thirteenth day.

Pathologic Report.—The specimen consisted of a large ovarian tumor, measuring 19 by 13 by 9 cm., and weighing 1,300 grams. The external surface was smooth and glistening. On section, the tumor was found to contain a large fetus

measuring from vault to coccyx 21 centimeters. Lying at the opposite end of the tumor and just beside the fetus, to which it was joined by the umbilical cord, was a placenta measuring 10 by 5 centimeters. Both fetus and placenta were encapsulated by a very thin wall, the inner lining of which was fairly smooth. The average thickness of the wall was 1½ millimeters. The fetus was well formed, and showed no gross abnormalities.

Sections of the other ovary which measured 6 by 5 by 4 cm. showed it to be cystic and thin-walled. It was found to be filled with clear serous fluid. The inner lining of the cyst was smooth and glistening. To one side could be seen a small portion of tissue which appeared to be atrophic ovarian tissue.

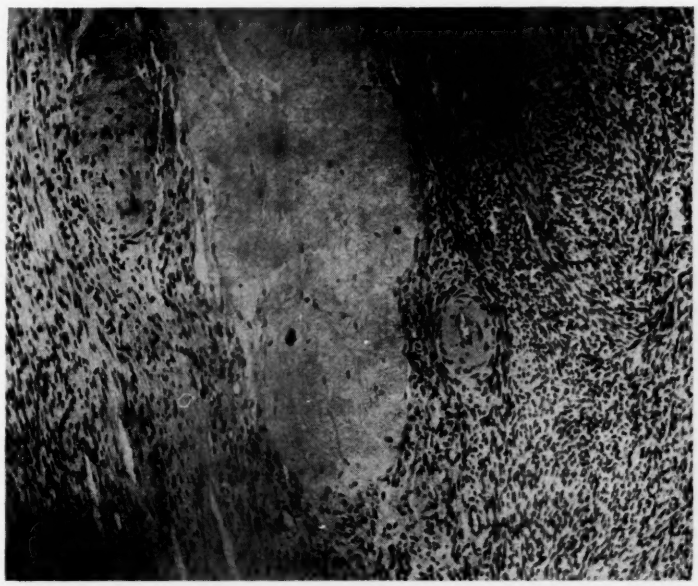


Fig. 3.—Section of capsule showing ovarian tissue and corpus albicans.

Microscopic.—Sections of the wall showed it to be composed of typical but compressed ovarian stroma containing a compressed corpus albicans. On the inner surface of one section could be seen numerous fragments of hairs embedded into the ovarian tissue. The surrounding tissue showed foreign body giant cell reaction. This portion of the wall unquestionably contained ovarian tissue. Repeated sections through the wall of the tumor showed the complete absence of epithelial lining and the constant presence of ovarian stroma. Some sections showed several glands lined by cuboidal and columnar epithelium. Sections of the other cyst showed it to be lined with very flattened epithelium which has ovarian stroma along one area.

Pathologic Diagnosis.—(1) Ovarian pregnancy, and (2) serous cyst of left ovary.

The patient was seen in the office six months later. She had had no bleeding since discharge from the hospital and was feeling well. Examination revealed nothing of note at this time.

It is felt this case meets all the criteria of true primary ovarian pregnancy.

Original Communications

IN VITRO FERTILIZATION AND CLEAVAGE OF HUMAN OVARIAN EGGS*

MIRIAM F. MENKIN, M.A.,† AND JOHN ROCK, M.D., BROOKLINE, MASS.

(From the Department of Gynecology, Harvard Medical School, and the Fertility Clinic Laboratory, Free Hospital for Women)

IN 1880, S. L. Schenk,[1] a Viennese embryologist, reported in some detail his experiments on in vitro fertilization of the ovarian eggs of the rabbit and the guinea pig. He described the first cleavage, as it occurred in vitro, and noted the inequality in size of the two resulting daughter cells. Some years later, Onanoff,[2] in a brief note published posthumously in 1893, mentioned that he had been able to induce in vitro fertilization and cleavage of uterine eggs of the rabbit and the guinea pig. He stated that the eggs had developed in vitro up to the eight-cell stage. Furthermore, this author reported that when ova fertilized in vitro were transferred to the abdominal cavity of another animal, whether male or female, of the same species, development continued until the embryos had attained the stage of the primitive streak. No details or photographs were furnished in connection with these experiments, nor has a careful survey of the literature discovered confirmation of these results by other investigators.

In 1930, Pincus[3] observed sperm penetration in tubal rabbit eggs inseminated in vitro. By transplantation of such eggs into the oviduct of a pseudopregnant rabbit which subsequently produced young, possessing the proper genetic characteristics, Pincus and Enzmann[4] in 1934 presented what they regarded as the "first certain demonstration that mammalian eggs can be fertilized in vitro." In the same year, Krassovskaja[5] reported continuous observations for many hours of in vitro fertilized tubal rabbit eggs. Forty-six hours after spermatozoa had been added to the egg, this author noted the development of the morula stage (twenty-eight cells). Subsequently, this same investigator[6] described in vitro fertilization and cleavage of tubal rabbit eggs that had been inseminated with rat spermatozoa.

In 1935, Pincus and Enzmann[7] transplanted into the Fallopian tubes of pseudopregnant rabbits ovarian eggs that had been inseminated in vitro. Two to three days later, regular cleavage was observed to have occurred in a small number of cases. Consequently, these investigators concluded that "normal fertilization can be secured with eggs removed from the follicles." As a final proof that true fertilization of mammalian ovarian eggs can occur in vitro, Pincus[8] in 1939 demonstrated that some ovarian rabbit eggs that had been exposed to spermatozoa in vitro possessed the diploid number of chromosomes.

Early cleavages in vitro have been observed in rabbit eggs that had been fertilized in vivo. Lewis and Gregory[9] obtained cinematographs of such eggs as they developed from the one- to the eight-cell stage. In the guinea pig, Squier[10] reported in vitro cleavage from the two- to the four-cell stage of four eggs that had been fertilized in vivo.

*This study has been aided by grants from the William F. Milton Fund of Harvard University, the Committee for Research in Problems of Sex, National Research Council, and the Carnegie Corporation of New York.

†Present address: Lankenau Hospital Research Institute, Philadelphia, Pa.

In vitro insemination experiments have also been performed with eggs of the mouse and rat.[11, 12] While certain effects of spermatozoal action were noted, such as dehiscence of follicle cells (in both mouse and rat eggs), as well as shrinkage in volume of the egg and second polar body formation (in the rat egg), cleavage was not reported in these studies.

In vitro cleavage of in vivo fertilized rat eggs was occasionally observed by Defrise[13] when the eggs were cultivated in certain media. Only one or two divisions were noted. In their comprehensive monograph on the mouse ovum, Lewis and Wright[14] include a photograph of an egg fertilized in vivo that divided into two cells in vitro.

To our knowledge, there have been no reports of in vitro fertilization of the eggs of higher mammals. In 1941, Lewis and Hartman[15] mentioned two unsuccessful attempts to fertilize tubal monkey eggs in vitro. Previously, these same investigators[16] had cultured in vitro from the two- to the eight-cell stage a monkey egg fertilized in vivo.

Most textbooks of embryology comment on our lack of knowledge of the fertilization and first cleavage stages of the human ovum. We have encountered in the literature only two references to the earliest stages of the human zygote. In 1944, Hamilton[17] reported in a fresh tubal egg removed from an operative case the presence of many spermatozoa in the zona pellucida, and toward the center of the egg a clear area containing "dark rodlike bodies suggestive of chromosomes on the spindle of first cleavage." However, since this specimen was lost before fixation, there is no proof that the egg was actually fertilized. Shortly afterwards, Hamilton[18] noted, in a fixed preparation of an unsegmented human tubal egg, many spermatozoa in the zona pellucida, and within the cytoplasm, two nuclei of unequal size, which he regarded as the pronuclei. This paper appeared in abstract form; so far, we have been unable to find a more detailed account.

In 1939, Pincus and Saunders[19] reported that about 30 per cent of human ovarian ova cultured in blood serum for intervals ranging between eight and one-half and twenty-four hours showed polar body formation and hence became theoretically susceptible to fertilization. On the basis of these findings, we have made numerous attempts to initiate in vitro fertilization of human ovarian eggs cultured for varying lengths of time. Utilizing the surgical material available at the Free Hospital for Women, we performed most of our experiments on eggs from ovarian tissue removed just prior to the expected time of ovulation. Nearly 800 human follicular eggs have been isolated and studied during the course of this investigation; of these, 138 have been observed after exposure to spermatozoa in vitro.*

Several factors were varied through the period of this study; e.g., the conditions of culture of the eggs, both before and after exposure to spermatozoa, the duration of contact of egg and spermatozoa, and the concentration of the sperm suspensions used. Employing a certain combination of these variables, we have been able to induce cleavage in three experiments. A condensed report of these findings has been published previously.[20]

In two of these cases (No. 20,768 and No. 14,518), the egg, after being subjected to certain procedures (to be described later), was found to be in the two-cell stage. In the third case (No. 21,012), two eggs divided. One of these, when first seen in cleavage, consisted of one large blastomere and two smaller ones, each of the three containing a round, vesicular body, which, at the time, we believed to be a nucleus. The second egg from this same patient was in a

*Most of the eggs studied were obtained by incising individual follicles, ranging in size from 3 mm. to about 3 cm. However, a few of the eggs were recovered by teasing pieces of ovarian tissue in a dish containing Locke's solution and allowing the ova to float into the surrounding fluid. The follicles from which these eggs originated were, as a rule, smaller than 3 mm. in diameter; in some cases, they were too small to be seen with the naked eye.

similar stage, but part of the cytoplasm appeared fragmented, and soon proceeded to undergo rapid, degenerative changes. In this report, as in the preliminary one,[20] we will therefore confine our discussion to the two eggs in the two-cell stage and the more normal appearing of the two eggs in the three-cell stage.

The Two-Cell Stage of the Human Egg

First Specimen.—The first specimen was obtained from a 38-year-old married woman (No. 20,768) who had had four labors, and was admitted to the hospital with a diagnosis of relaxed perineum, lacerated, cystic, eroded cervix, and prolapse. At operation, on the tenth day of the cycle, a complete hysterectomy and right salpingo-oöphorectomy were performed. Cycles immediately preceding operation had been, respectively, twenty-seven, twenty-three, forty-seven, and twenty-eight days. The endometrium was found to be in the late proliferative stage.

The egg was recovered free in the follicular fluid drained from a bluish follicle, 2.3 cm. in diameter, in the extirpated right ovary, about one hour after oöphorectomy. When first observed, the ovum was within a moderate investment of granulosa cells. After rapid transfer through three portions of sterile Locke's solution, it was pipetted into a Carrel flask containing 3 c.c. of serum prepared from the blood of the egg donor.* The blood had been taken from the patient after the operation. The egg was then placed in the incubator at 37.5° C. It had been at room temperature for about three hours; i.e., the time elapsing since oöphorectomy.

After twenty-seven hours of culture, the preparation was removed from the incubator and examined. The compact granulosal investment, which had surrounded the egg on the previous day, now appeared as a loose meshwork of shrunken, degenerated, granulosa cells. The egg was rapidly transferred through small amounts of Locke's solution in three watch glasses. In the third watch glass were then pipetted a few drops of the so-called "fertilizing suspension" of spermatozoa. This had been prepared as follows:

Seven-tenths of 1 c.c. of a semen specimen one and one-half hours old (in which 95 per cent of the spermatozoa were highly motile) was pipetted into a centrifuge tube and the volume brought to 2 c.c. with sterile Locke's solution. After being mixed, the suspension was centrifuged for fifteen minutes at full speed.† The supernatant fluid was then decanted, and to the firm white sediment was added Locke's solution, again to a volume of 2 c.c. The sediment was diffused in the medium by gently drawing the former in and out of a pipette. Centrifugalization and decantation were repeated, and then to the washed sediment was added Locke's solution to a volume of 0.2 c.c.; i.e., about one-third the original volume of the semen used. A hanging-drop of this suspension showed high concentration and activity. At the time when the spermatozoa were added to the egg, the former had been at room temperature for two hours and forty-five minutes; i.e., the interval since ejaculation.

The watch glass containing the ovum and spermatozoa was left on the stage of the dissecting microscope at room temperature for one hour, the egg being kept in constant view (at a magnification of ×35). The spermatozoa showed great activity throughout the period of observation; they were clearly seen to travel through the interstices of the loose cellular formation surrounding the egg, and many were noted in active motion around the zona pellucida.

*In all the experiments reported here, the serum used for culture of the eggs prior to exposure to spermatozoa was that of the patient who had furnished the eggs, while subsequent culture (following contact with spermatozoa) was carried out in serum of any patient willing to donate blood.

†About 3,500 revolutions per minute; an International Clinical Centrifuge with a No. 804 angle head was used.

At the end of one hour, the ovum, along with some of the surrounding sperm suspension, was transferred to a Carrel flask containing 3 c.c. of serum of a 51-year-old patient who had been admitted to the hospital because of dysfunctional flowing. The blood had been obtained from the patient about six hours before the egg was placed in the serum. As the egg was pipetted into the Carrel flask, the loose formation of degenerated cells surrounding it suddenly dropped off, and it appeared as a single round cell with a fuzzy border.

When it had been cultured for forty and one-half hours, the ovum was washed out of the Carrel flask into a watch glass with Locke's solution.* In the plane of examination under the dissecting microscope, it now appeared to consist of two equal, spheroid blastomeres, each measuring 86μ in diameter, and was enclosed within a zona pellucida of uniform thickness, measuring 14μ.

A sketch of the egg was made under the compound microscope (Fig. 1*A*). Now the blastomeres appeared elliptic. At this time, a slight inequality in size of the blastomeres was noted. The ovum was then gradually fixed in Bouin's fluid by removing the surrounding medium (Locke's solution) and substituting the fixative, drop by drop. Fifteen minutes after the start of fixation, the ovum had undergone considerable shrinkage (to almost one-half its original volume). Dehydration had nearly been completed when the egg, unfortunately, was lost.

The Follicle Wall.—For several reasons, it seems worth while to include in this report a photomicrograph of the stained section of the follicle from which this egg was obtained (Fig. 1*B*). In the first place, it is the only one in our large collection of so-called "preovulatory" human follicles which we are certain contained a fertilizable ovum at the time the section was taken; i.e., it is the only section in existence, as far as we know, of a human ovarian follicle which can be exactly dated with respect to subsequent fertilization of the egg derived from it. The time interval between fixation of this follicle and insemination of the egg was twenty-nine and one-half hours.

In section, the convoluted wall of this follicle shows the three typical layers: granulosa, theca interna, and theca externa. The inner, or granulosa layer, is composed of small, polyhedral, dark-staining cells in which mitoses are prominent. The basal layer is more closely packed and the nuclei are more cylindric with their vertical axes arranged perpendicularly to the follicle wall. There is some focal separation (?artifactual) of the granulosa and theca interna. The latter is well vascularized, congested, and composed of cells which are larger, paler and more irregular than those of the granulosa. Mitoses are seen in the theca interna, but not as frequently as in the granulosa cells. The theca externa cells are cylindric or stellate and separated by variable amounts of edema fluid. It appears as though luteinization has just begun in the theca interna, but not within the granulosa cells. Apparently, then, this follicle represents a typical "preovulatory" stage; i.e., a mature follicle that is just about to rupture.†

Second Specimen.—Of the second egg in the two-cell stage we have a complete series of stained sections. Essentially the same procedure as described above was carried out on an ovum, washed from a follicle of a 31-year-old para vi, gravida viii (No. 14,518), who was admitted to the hospital with a diagnosis

*According to our usual technique, the eggs are pipetted out of the Carrel flask. In this case, however, it was not possible to identify the egg through the wall of the flask, as some contamination of the medium had occurred, probably due to the fact that in transferring the egg to the Carrel flask part of the sperm suspension had been carried along with it. Contamination of the medium was also noted in the third experiment to be described, where the same procedure was followed, but not in the second experiment. In the latter case, the egg was washed several times before transference to fresh serum.

†We are indebted to Doctor Arthur T. Hertig for this description of the histology of the follicle wall.

of cystocele, rectocele, and retroverted, prolapsed uterus. A complete hysterectomy and right salpingo-oöphorectomy were performed on the eleventh day of the cycle. The endometrium was in the late proliferative phase of its development. The last two cycles preceding operation had been, respectively, twenty-eight and thirty-four days long.

Twelve eggs were recovered from the extirpated right ovary by incising and flushing the follicles, and one from follicular fluid obtained by aspiration in situ of follicles of the left ovary. Since the follicles visible in the right ovary were closely approximated on the surface, it was not possible to identify the one from which any particular egg was derived. Although twelve eggs in all (one was lost) were carried through the entire procedure and exposed to the same technique, only one of them divided.

This ovum was one of a set of four, of which three, when first seen, were covered by a thick granulosa cell investment, and one by only a few rows of cells. The eggs were washed twice in Locke's solution, and were then transferred to a Carrel flask containing 3 c.c. of serum that had been prepared from blood taken from the egg donor twenty-two hours previously. The preparation was then placed in the incubator at 37.5° C. At this time, the eggs had been at room temperature for about three and one-half hours; i.e., the interval since oöphorectomy.

After twenty-two and one-half hours' incubation, the eggs were washed once in Locke's solution and exposed for two hours at room temperature to a sperm suspension prepared from the same donor and in essentially the same manner as in the first case reported above. At the time when the spermatozoa were added to the eggs, the former had been at room temperature for three hours; i.e., the interval since ejaculation. The ova were then washed twice in Locke's solution and transferred to a Carrel flask containing 3 c.c. of serum prepared from blood that two hours previously had been given by a 62-year-old patient with carcinoma of the cervix uteri. The preparation was then incubated for forty-five hours at 37.5° C.

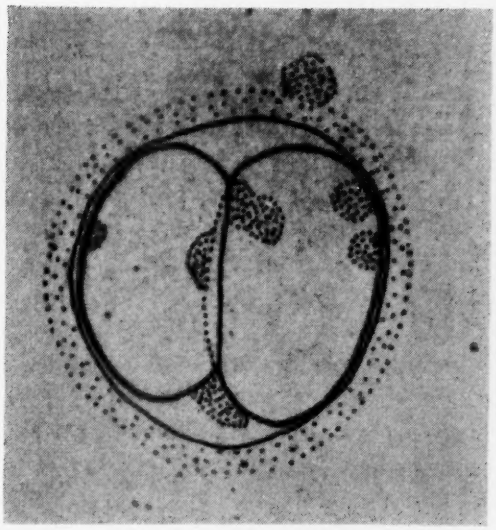
When examined at the end of the incubation period, the egg, as observed through the wall of the flask, was found to be in the two-cell stage. A photograph (Fig. 2*A*), made of the specimen two hours later, shows it to resemble very closely the first egg recovered in the same stage (Fig. 1*A*). Two "biscuit-

---

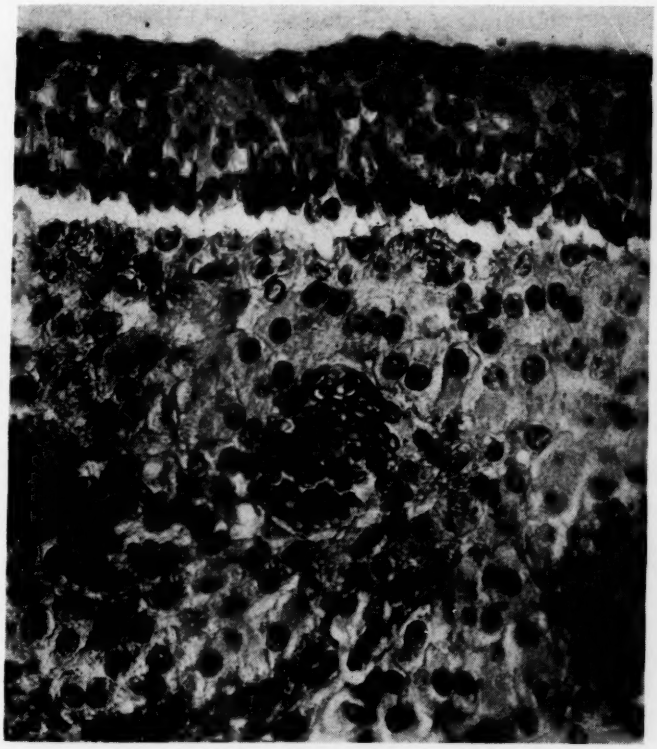
Fig. 1.—No. 20,768. Human egg in two-cell stage: *first specimen.* This egg was recovered free in the fluid drained from a 2.3 cm. ovarian follicle of a 38-year-old white woman after laparotomy on the tenth day of the cycle. After having been washed in Locke's solution, the ovum was cultured for twenty-seven hours at 37.5° C. in the serum of the same patient. It was again washed in Locke's solution and was exposed in vitro for one hour at room temperature to a washed concentrated suspension of human spermatozoa in Locke's solution. It was then transferred to serum from a 51-year-old female patient and incubated. After forty and one-half hours of culture, the egg was found to be in the two-cell stage, and a sketch was made of it. The specimen was then fixed, but was lost during dehydration.

A. Free-hand sketch of egg under high power of the compound microscope (after forty and one-half hours of culture).

B. Convoluted wall of mature Graafian follicle from which the egg was recovered. Insemination of the egg took place twenty-nine and one-half hours after the follicle wall was fixed. Section showing granulosa, theca interna, and theca externa. There is some focal separation (? artifactual) between the granulosa and the theca interna. In the theca interna, there is considerable vascularization and congestion. Note large, pale-staining cells of the theca interna, as contrasted with the small, polyhedral, dark-staining cells of the granulosa. Mitoses are seen in the theca interna, but not as frequently as in the granulosa cells. The theca externa cells are cylindric and stellate and are separated by variable amounts of edema fluid. It appears as though luteinization had just begun in the theca interna, but not in the granulosa cells. Fixed in Bouin's solution; embedded in paraffin; sections cut at 6μ, and stained with hematoxylin and eosin. (×400.)



A.



B.

Fig. 1.—*(See legend on opposite page.)*

shaped''* blastomeres of slightly unequal size, containing granular cytoplasm, are enclosed within the zona pellucida. Numerous spermatozoa are present, some along the border and at least one within the zona.

The entire egg (including the zona pellucida) measured 153μ by 155μ; the vitellus was 100μ by 113μ, and the average thickness of the zona pellucida was 23μ. The blastomeres measured 88μ by 58μ, and 105μ by 58μ, respectively.†

The egg, transferred to a plasma drop, was fixed according to the method described by Pincus.[8] The plasma drop was warmed for one-half hour under an electric light bulb. The resulting clot was then carried through the double embedding celloidin-paraffin method, serially sectioned at 8μ, and stained with hematoxylin and eosin.

Since the ovum is included in eight sections, its total thickness after fixation is approximately 64μ. A section through the middle of the specimen (Fig. 2*B*) measures 50μ by 75μ (excluding the imperfect zona). The blastomeres (designated, for convenience as ''A'' and ''B,'' from left to right) measure 63μ by 39μ, and 66μ by 36μ, respectively. The cytoplasm appears uniformly granular, with the exception of the polar regions where there is beginning vacuolization, as had been noted in the fresh specimen immediately following photography. In the approximate center of each cell, there is a round, vesicular nucleus containing a chromatin meshwork. The nucleus in blastomere ''A'' measures 18μ by 13μ, and that in blastomere ''B,'' 16μ by 15μ. The zona pellucida surrounds the egg over about two-thirds of its circumference. Failure to retain the entire zona pellucida in section was doubtless due to the method of fixation; as seen in Fig. 2*A*, it had been intact in the fresh specimen. In a clearly defined portion (near ''1 o'clock''), the zona measures 7μ to 8μ across. Several dark bodies suggestive of sperm heads may be identified on the photograph; one of them appears to be just within the cell body of blastomere ''B'' (near ''1 o'clock'').

The section adjacent to the one described above, and represented in Fig. 2*C*, was, unfortunately, torn during cutting and is reproduced only to show the polar body near ''11 o'clock,'' beside blastomere ''A.'' The polar body measures 18μ by 10μ, and contains what appears in the photograph as a group of chromatin units discrete enough to be counted. However, when the photograph is magnified twelve times, we see the chromatin in the form of a lobulated body, only two clumps being definitely separated from the general mass. Opposite blastomere ''B'' (at about ''3 o'clock'') two dark bodies resembling sperm heads are seen. Other sections of this egg show one, five, seven, and nine such bodies, respectively.

*The so-called "biscuit" shape is characteristic of the blastomeres of other mammalian eggs in the two-cell stage.[10] Inequality of the daughter cells during early cleavages has been noted in the monkey egg,[16] as well as in the eggs of the rabbit and guinea-pig,[1] the rat,[12] the mouse,[11] and other mammals.[21] The larger cell divides first, thus accounting for the occasional finding of an egg in the three-cell stage, as shown in Fig. 3.

†In both this specimen and in that of the three-cell stage (to be described below), the sum of the dimensions of the individual components of the egg in each diameter, as listed, does not equal the dimensions of the egg as a whole in that particular diameter. There are two reasons for this discrepancy. First, the measurements in each diameter of the vitellus and of the individual blastomeres were taken through their respective centers, rather than through the middle of the egg as a whole; i.e., along a slightly different axis. This was done in order to compare the dimensions of the fresh with the fixed preparation of each egg; in neither of the fixed preparations was the egg surrounded by an intact zona. The numerical discrepancy noted here is also due in part to the presence of a shrinkage space (perivitelline space) between the vitellus and the zona. The failure of the vitellus to fill the entire zonal cavity is characteristic of other mammalian eggs after ovulation.[15]

The Three-Cell Stage

The third experiment to be reported was performed on ova of a 38-year-old patient (No. 21,012), in whom the diagnosis of tuberculous endometritis had been made after routine biopsy taken in the course of an investigation for sterility. Operation, which consisted of complete hysterectomy, right oöphorectomy, and bilateral salpingectomy, was performed on the twelfth day of the cycle. The endometrium was found to be in the late proliferative stage. The two cycles immediately preceding operation had been thirty days long. Tissue examination showed the uterus and tubes to be extensively involved by the tuberculous process; both tubes were sealed and the fimbriae were inverted.

Four eggs, recovered in washings of incised follicles, were subjected to essentially the same procedures as outlined above. After such treatment, two of them were found in the three-cell stage.

These eggs were obtained from two medium-sized follicles in the right ovary, about four and one-half hours following oöphorectomy. After having been washed three times in Locke's solution, the ova were transferred to a Carrel flask containing 3 c.c. of serum prepared from blood that had been obtained from the egg donor four hours previously. The preparation was then placed in the incubator at 37.5° C. At this time, the ova had been at room temperature for about five hours; i.e., the interval since oöphorectomy.

After twenty-seven hours of incubation, the eggs were washed three times in Locke's solution and were then exposed to a sperm suspension prepared from the same donor and in essentially the same manner as in the two experiments described above. At the time when the spermatozoa were added to the egg, the former had been at room temperature for four and one-half hours; i.e., the interval since ejaculation.

After having been in contact with the spermatozoa for one hour and ten minutes at room temperature, the ova, along with some of the surrounding sperm suspension, were transferred to a Carrel flask containing 3 c.c. of serum prepared from blood that had been given about eight hours previously by a 53-year-old postmenopausal patient. The eggs were then incubated for forty-six hours at 37.5° C.

At the end of this period, since the ova could not be identified in the flask because of some contamination, the contained fluid was emptied into a watch glass, and sketches of the eggs were made under the high power of the compound microscope.

At this time, the more normal of the two specimens consisted of three round, regular blastomeres, two of nearly equal size, and one definitely larger. In each of them we observed a round, vesicular body which, at the time, we believed to be a nucleus. Within the next two hours, the egg, kept at room temperature, appeared distorted. At the moment, we regarded this as a degenerative phenomenon, but later we were reminded that Lewis and Hartman[16] had noted such distortion in the dividing monkey egg during each of several early cleavages. A photograph of the egg (Fig. 3*A*), taken about two hours after it had been removed from the incubator, bears a striking resemblance both to the monkey egg (cf. Lewis and Hartman[16]—Plate 1, Fig. 9) and to the mouse egg (cf. Lewis and Wright[14]—Plate 2, Fig. 15) in a similar stage. In our human egg, as in the mouse and monkey eggs, the second cleavage plane is at right angles to the first one. The bulge at "5 o'clock" is believed to represent a polar body. The two pale round formations in the center of the egg may also be polar bodies (cf. Lewis and Wright[14]—Plate 2, Fig. 17). At least five dark objects assumed to be spermatozoa may be identified in the zona pellucida.

The entire egg (including the zona pellucida) measured 170μ by 183μ; the vitellus was 103μ by 127μ, and the zona pellucida averaged 21μ in thickness. The largest blastomere measured 97μ by 73μ, and the two smaller ones, 62μ by 62μ, and 50μ by 63μ, respectively.

The ovum was fixed, serially sectioned, and stained in the same manner as the second egg, described above. Since it includes ten sections, cut at 8μ, the specimen is approximately 80μ thick, again a shrinkage of about 50 per cent, attributable to fixation. A section through the middle of the egg measures 50μ by 86μ (Fig. 3*B*). The largest blastomere is here seen to measure 66μ by 49μ, and the two smaller ones, 35μ by 38μ, and 33μ by 44μ, respectively. Several round bodies are noted in the largest blastomere. These are shown more clearly in another section (Fig. 3*C*) in which they are seen to be present in each of the three blastomeres. They are probably nucleoli, similar to those observed in the corresponding stage of the mouse egg fertilized in vivo (cf. Lewis and Wright[14]—Plate 2, Fig. 15).

In a third section (Fig. 3*D*), there is a structure at "11 o'clock," measuring 14μ by 9μ, which is strongly suggestive of a polar body. Nowhere throughout the preparation is there any sign of the zona pellucida; this had evidently been dissolved by the fixative.

Comparison of Two- and Three-Cell Human Eggs With Similar Stages of Other Mammalian Eggs

In regard to the duration of early cleavage stages, it is pertinent to cite the report of Lewis and Hartman[16] on the culture in vitro of the monkey egg fertilized in vivo. In their experiment, in which fertilization was believed to have occurred soon after ovulation, the minimum duration of the one- and two-cell stages was thought to be thirty-six and one-half hours. We observed two eggs in the two-cell stage forty and one-half and forty-five hours, respectively, following contact with spermatozoa. Since, in the monkey egg studied

---

Fig. 2.—No. 14,518. Human egg in two-cell stage: *second specimen.* This egg was washed out of an ovarian follicle of a 31-year-old white woman after laparotomy on the eleventh day of the cycle. After having been washed in Locke's solution, the egg was cultured in the patient's serum for twenty-two and one-half hours, was again washed in Locke's solution, and was exposed in vitro for two hours at room temperature to a washed suspension of human spermatozoa in Locke's solution. It was then washed in Locke's solution and incubated for forty-five hours at 37.5° C. in serum from a 62-year-old female patient.

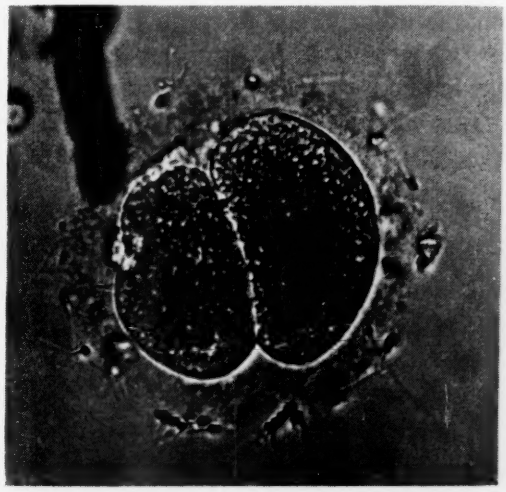
A. Photograph of egg (after forty-five hours' incubation) showing two blastomeres within zona pellucida. At the margin of the latter are numerous spermatozoa, and at least one is seen within the zona. The entire egg (including the zona pellucida) measured 153μ by 155μ; the vitellus was 100μ by 113μ, and the average thickness of the zona was 23μ. The blastomeres measured 88μ by 58μ, and 105μ by 58μ, respectively. (×300.) (Cf. Lewis and Hartman[16]—Plate 1, Fig. 7, and Lewis and Wright[14]—Plate 1, Fig. 10, for similar stages of monkey and mouse egg, respectively.)

B. Section through the middle of the egg. The egg, transferred to a plasma drop, was fixed with Bouin's solution, and the plasma drop was dried by warming it under a lamp. The resulting clot was carried through the double embedding celloidin-paraffin method, serially sectioned at 8μ, and stained with hematoxylin and eosin. Two blastomeres (one slightly larger than the other), containing granular cytoplasm, are enclosed within a zona pellucida which surrounds the egg over about two-thirds of its circumference. Failure to retain the entire zona in section is ascribed to the method of fixation. Several dark bodies suggestive of sperm heads may be identified; one of them appears to be just within the cell body of blastomere "B" (near "1 o'clock").

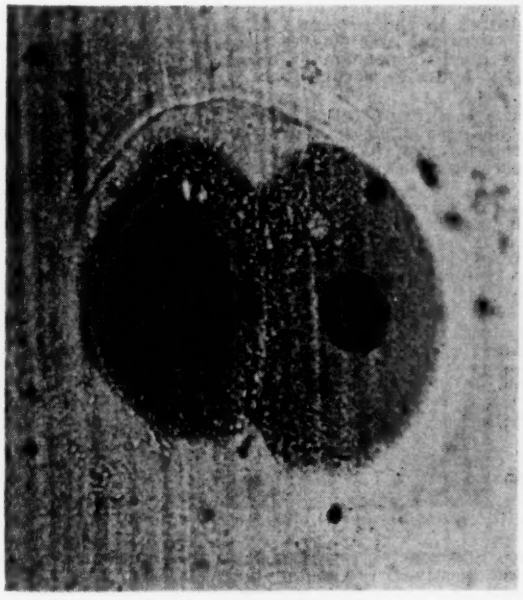
Since the egg is included in eight sections, its total thickness after fixation is ca. 64μ. This section, excluding the imperfect zona, measures 50μ by 75μ. The blastomeres, designated, for convenience, as "A" and "B," from left to right, measure 63μ by 39μ, and 66μ by 36μ, respectively. The nucleus in "A" measures 18μ by 13μ, and that in "B," 16μ by 15μ. In a well-defined portion (near "1 o'clock"), the zona measures 7μ to 8μ across. (×600.)

C. Another section of the same egg, adjacent to the one described above. This section, torn during cutting, is reproduced to show (besides blastomere "A") a polar body, measuring 18μ by 10μ, and containing chromatin units, two of which are clearly demarcated from the general mass. (×500.)

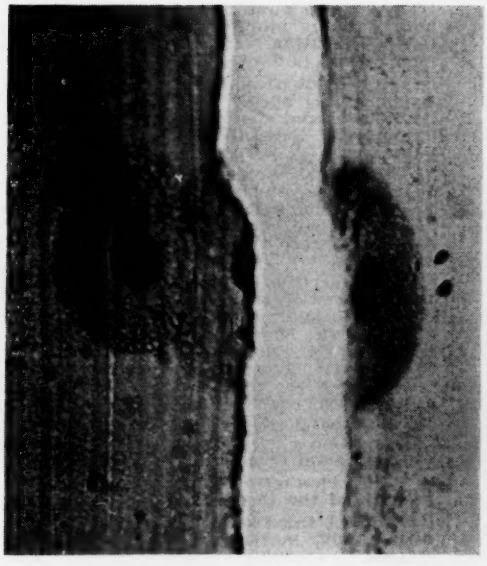
by Lewis and Hartman, the three-cell stage lasted less than one hour, the four-cell stage began at least thirty-seven and one-half hours, and ended at least forty-six and one-half hours following fertilization. Our two eggs were seen in the three-cell stage forty-six hours after exposure to spermatozoa. As Lewis and Hartman point out, a correction of two hours should be applied to their figures, since the egg was at room temperature for this period. On the other hand, since their values are "minimum" ones, the difference in the time relations between their results and ours cannot be regarded as a significant one.



A.



B.



C.

Fig. 2.—*(See legend on opposite page).*

In a study of in vivo fertilized mouse eggs removed at different intervals after copulation, Lewis and Wright[14] have found similar time relations to prevail: duration of one-cell stage, none to twenty-four hours; duration of two-cell stage, twenty-four to thirty-eight hours, and of three- and four-cell stage, thirty-eight to fifty hours. Hence, our findings in this respect are in general agreement with those reported for the mouse, as well as for the monkey egg. In evaluating these figures, one should of course bear in mind the probability, as pointed out by Lewis and Hartman,[16] that the duration of cleavage stages is longer in vitro than in vivo.

In the rabbit, on the other hand, cleavage of the fertilized egg proceeds at a much faster rate.[9, 22] Krassovskaja[5] reported that the first cleavage of the rabbit egg began sixteen hours and forty minutes after spermatozoa had been added in vitro, and was completed forty-five minutes later; i.e., seventeen and one-half hours after insemination. The four-cell stage was attained twenty hours after the addition of spermatozoa to the egg. By the forty-sixth hour following in vitro insemination, Krassovskaja observed the 28-cell stage (morula). As has been noted above, our two human eggs, at a corresponding interval following insemination, had reached only the three-cell stage.

Fig. 3.—No. 21,012. Human egg in three-cell stage. This egg was washed out of an ovarian follicle of a 38-year-old sterility patient on the twelfth day of the cycle. After having been washed in Locke's solution, the egg was cultured in the patient's serum at 37.5° C. for twenty-seven hours, was again washed in Locke's solution, and was exposed in vitro for one hour and ten minutes at room temperature to a washed suspension of human spermatozoa in Locke's solution. It was then cultured for forty-six hours in serum from a 53-year-old postmenopausal patient.

A. Photograph of the egg (after forty-six hours of culture, followed by two hours at room temperature) shows it to have undergone definite changes since it was first seen in cleavage. Shrinkage and distortion in shape occurred in the interim, as well as vacuolization of the cytoplasm. Several dark bodies suggestive of spermatozoa are well defined within the zona pellucida.

The entire egg (including the zona pellucida) measured 170μ by 183μ. The vitellus was 103μ by 127μ, and the zona pellucida averaged 21μ in thickness. The largest blastomere measured 97μ by 73μ, and the two smaller ones, 62μ by 62μ and 50μ by 63μ, respectively. The bulge at "5 o'clock" probably represents a polar body (cf. Lewis and Hartman[16]—Plate 1, Fig. 9, monkey egg). The two round pale objects in the center of the egg may also be polar bodies (cf. Lewis and Wright[14]—Plate 2, Fig. 17, mouse egg). (×300.)

B. Section through the middle of the same egg. The egg, transferred to a plasma drop, was fixed with Bouin's solution, and the plasma drop was warmed. The resulting clot was carried through the double embedding celloidin-paraffin method, serially sectioned at 8μ, and stained with hematoxylin and eosin. Three blastomeres are well defined, the two smaller ones being nearly equal in size. Note round bodies in the largest blastomere; these are probably nucleoli (cf. Lewis and Wright[14]—Plate 2, Fig. 15, mouse egg). The absence of the zona pellucida in the sections is doubtless due to the method of fixation, as it had been clearly seen in the fresh specimen.

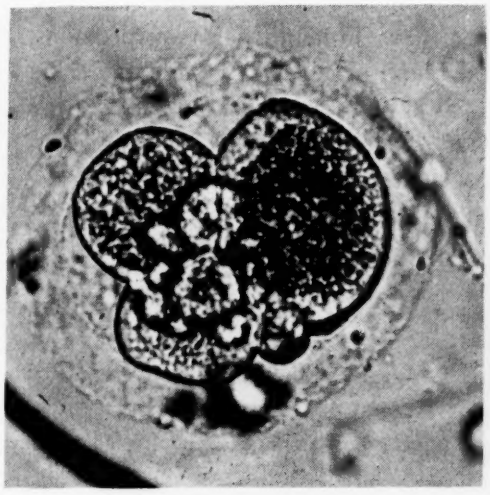
Since there are ten sections, cut at 8μ, the entire fixed egg is approximately 80μ thick. This section measures 50μ by 86μ. The largest blastomere is here seen to be 66μ by 49μ, and the two smaller ones, 35μ by 38μ, and 33μ by 44μ, respectively. (×400.)

C. Another section of the same egg, showing the nucleoli more clearly. Here these appear in each of the three blastomeres. (×500.)

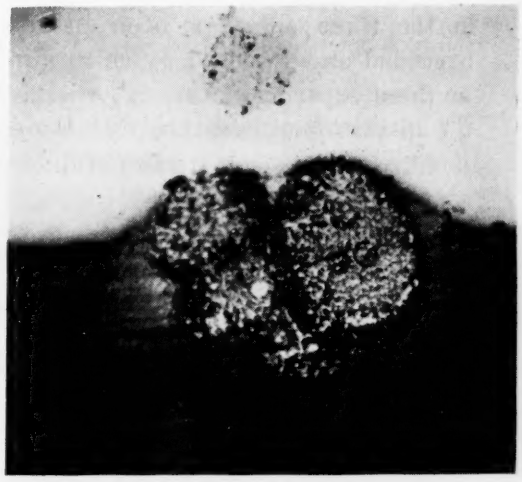
D. A third section of the same egg. Only two blastomeres are present in this section. An ovoid body, measuring 14μ by 9μ, and strongly suggestive of a polar body, is seen at "11 o'clock." (×500.)

It is also of interest to compare the sizes of our human eggs with those of single mouse and monkey eggs in comparable stages, as illustrated in the respective monographs of Lewis and Wright[14] and of Lewis and Hartman.[16] The following figures were obtained by averaging the horizontal and vertical diameters of single and similar eggs (as represented in their respective photographs).*

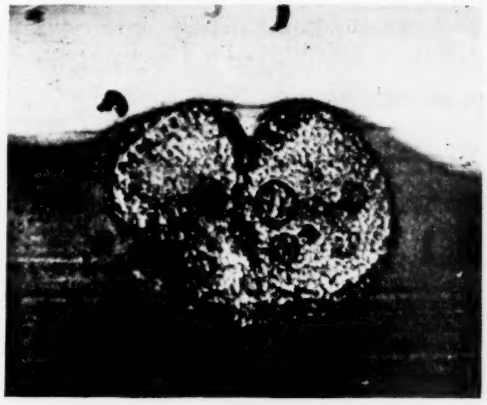
	MOUSE	MONKEY	MAN
Two-cell stage	*101μ* (Plate 2, Fig. 13)[14]	*153μ* (Plate 1, Fig. 7)[16]	*154μ* (Fig. 2*A*, This Paper)
Three-cell stage	*105μ* (Plate 2, Fig. 15)[14]	*145μ* (Plate 1, Fig. 9)[16]	*177μ* (Fig. 3*A*, This Paper)



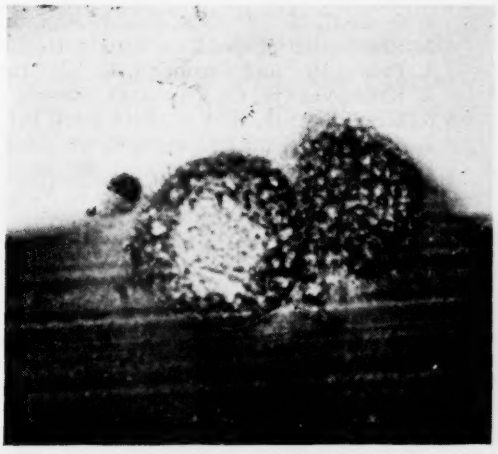
A.



B.



C.



D.

Fig. 3.—*(See legend on opposite page.)*

*In evaluating these figures, it should be noted that appreciable variation in the size of eggs of a particular stage has been reported in several species.

In regard to the thickness of the zona pellucida, the average value for the mouse egg, in both the two-cell stage (36 eggs) and in the four-cell stage (fifteen eggs), as computed from figures listed by Lewis and Wright,[14] is 11.5μ. Calculations made from data tabulated by Lewis and Hartman[15] show the average thickness of the zona pellucida in tubal monkey eggs to be 11.2μ for the two-cell stage (three eggs), and 16.5μ for the four-cell stage (two eggs). The zona pellucida in our human eggs measured 14μ and 23μ, respectively, for the two eggs of the two-cell stage, and 21μ for the three-cell egg. Whether or not these figures have any significance cannot be ascertained until more human specimens are available.

Summary

Two human ovarian eggs were found to be in the two-cell stage, and two in the three-cell stage, after in vitro exposure to human sperm suspensions, preceded and followed by culture in human blood serum. The time relations in these experiments are in general accord with those reported previously for the in vivo fertilized tubal monkey egg cultured in vitro, as well as for in vivo fertilized mouse eggs studied at different intervals after copulation.

We very gratefully acknowledge the invaluable advice and encouragement generously given us by Doctor Gregory Pincus, as well as the helpful assistance furnished at various stages by Doctor Nicholas T. Werthessen, Miss Lotte Lee Sichel, Miss Eleanor C. Adams, Mr. James M. Snodgrass, Doctor Stephen Fleck, and Doctor Harold Brown. We are also deeply indebted to Doctor Austin M. Brues for his help in the early part of the investigation, and to Doctor Arthur T. Hertig for his constant encouragement, advice, and material aid through his grant from the Carnegie Corporation of New York. We are grateful also to Doctor Warren H. Lewis of the Wistar Institute of Anatomy and Biology for reviewing this report.

The sections of two of the eggs described in this paper are in the custody of the Department of Embryology, Carnegie Institution of Washington, Baltimore, Maryland. The two-cell egg is labeled Carnegie No. 8260, and the three-cell egg is Carnegie No. 8500.1.

References

1. Schenk, S. L.: Mitt. aus d. embryol. Inst. Wien **1**: 107, 1880.
2. Onanoff, M. J.: C. R. Soc. de Biol. **5**: 719, 1893.
3. Pincus, G.: Proc. Roy. Soc., s. B., London **107**: 132, 1930.
4. Pincus, G., and Enzmann, E. V.: Proc. Nat. Acad. Sci. **20**: 121, 1934.
5. Krassovskaja, O. V.: Arch. Russes d'Anat., d'Hist. et d'Embryol. **13**: 415, 1934.
6. Krassovskaja, O. V.: Acta Zool. **16**: 449, 1935.
7. Pincus, G., and Enzmann, E. V.: J. Exper. Med. **62**: 665, 1935.
8. Pincus, G.: J. Exper. Zool. **82**: 85, 1939.
9. Lewis, W. H., and Gregory, P. W.: Science **69**: 226, 1929.
10. Squier, R. R.: Carnegie Inst. Wash. Pub. No. 433, Contrib. Embryol. No. 137 **23**: 223, 1932.
11. Long, J. A.: Univ. Cal. Pub. Zool. **9**: 105, 1912.
12. Gilchrist, F., and Pincus, G.: Anat. Rec. **54**: 275, 1932.
13. Defrise, A.: Anat. Rec. **57**: 239, 1933.
14. Lewis, W. H., and Wright, E. S.: Carnegie Inst. Wash. Pub. No. 459, Contrib. Embryol. No. 148, **25**: 113, 1935.
15. Lewis, W. H., and Hartman, C. G.: Carnegie Inst. Wash. Pub. No. 525, Contrib. Embryol. No. 180, **29**: 7, 1941.
16. Lewis, W. H., and Hartman, C. G.: Carnegie Inst. Wash. Pub. No. 443, Contrib. Embryol. No. 143, **24**: 187, 1933.
17. Hamilton, W. J.: J. Anat. **78**: 1, 1944.
18. Hamilton, W. J.: J. Anat. **80**: 224, 1946.
19. Pincus, G., and Saunders, B.: Anat. Rec. **75**: 537, 1939.
20. Rock, J., and Menkin, M. F.: Science **100**: 105, 1944.
21. Hamilton, W. J.: Proc. Roy. Soc. Med. **35**: 643, 1942.
22. Gregory, P. W.: Carnegie Inst. Wash. Pub. No. 407, Contrib. Embryol. No. 125, **21**: 141, 1930.

AN EVALUATION OF THE VAGINAL SMEAR METHOD FOR THE DIAGNOSIS OF UTERINE CANCER*

LEWIS C. SCHEFFEY, M.D., A. E. RAKOFF, M.D., AND JACOB HOFFMAN, M.D.
PHILADELPHIA, PA.

WITH THE TECHNICAL ASSISTANCE OF DOROTHY MEYERS

(From the Department of Obstetrics and Gynecology, Jefferson Medical College and Hospital)

ALMOST two decades have elapsed since Papanicolaou[1] first pointed out that exfoliated cancer cells shed from a uterine malignant growth could be found and recognized in smears prepared from the vaginal secretion. It has been only in the last five years, however, that this observation has received widespread attention as a diagnostic procedure for the detection of uterine cancer. In 1943 Papanicolaou and Traut[2] published their monograph on the "Diagnosis of Uterine Cancer by the Vaginal Smear" based on the examination of smears from 3,014 women, of whom 179 were found to have cancer which was primary in the uterus. Much interest was aroused by this work because of the high degree of accuracy which was claimed for the method as well as the excellent descriptions and colored plates of the various cells which could be found in the vagina in normal patients, in those with various functional abnormalities, and in patients with uterine carcinoma. It was apparent from their studies that the successful application of this method necessitated considerable experience, since the cytologic changes in the cells which one might encounter in such smears are most variable. It is not remarkable therefore, that although interest in the subject has been keen, the general application of this method necessarily has been slow. The several reports which have since appeared, particularly those by Meigs and his associates;[3] Fremont-Smith and associates;[4, 5] Jones, Neustaedter, and Mackenzie;[6] as well as Ayre,[7] have been quite enthusiastic and have encouraged others to make use of this diagnostic aid. Our own experience with this technique is now of four years' standing, and covers approximately five thousand cases, which include patients in the gynecologic wards and clinics of the Jefferson Hospital, patients from the private practices of our staff, and from women attending various Health Maintenance and Cancer Prevention-Detections clinics throughout the city of Philadelphia. During the course of our work, the advisablitiy of running a carefully controlled study on all patients admitted to the gynecologic wards became apparent. The purpose of this study was to determine the value of the vaginal smear as a routine procedure for the diagnosis of uterine cancer in gynecologic patients admitted to the ward.

*Aided by a grant from the Ortho Research Foundation, Raritan, New Jersey.
Read before The Philadelphia Obstetrical Society, May 1, 1947.

Procedure and Methods

During the course of this study, vaginal smears for cytologic examination were taken on all patients admitted to the gynecologic wards, usually within forty-eight hours of their admission, care being exercised not to take smears within twenty-four hours of a vaginal douche or other procedures which might interfere with the collection of the material or staining reaction. The smears were taken by a single technician who had several years of training in this work; if any difficulties were encountered she was assisted by the resident on the service. The technique employed was essentially that described by Papanicolaou and Traut. A slightly curved glass pipette attached to a strong rubber bulb was introduced into the posterior fornix of the vagina. As aspiration was in progress the tip of the pipette was rotated into all portions of the posterior vagina in order to obtain a representative sample. When the pipette was withdrawn the secretion was blown onto the surface of two clean glass slips. The material was then further spread with the convex side of the pipette and immediately dropped into a Coplin jar containing equal parts of 95 per cent alcohol and ether, special care being taken to prevent drying before fixation. The smears were taken to the laboratory and the preparation of the slides was completed promptly, employing the techniques described by Papanicolaou. One slide was prepared with stain EA 31, and the other with stain EA 36,* since somewhat different staining reactions often afford additional information. Each slide was read at least twice, and all abnormal or unusual cells were marked with a finder for further review, if necessary. For purposes of this study it was decided to classify each slide as positive or negative and to omit the designation of doubtful for statistical evaluation. This decision was reached because in many instances it would not have been possible to obtain repeat smears because of intervening surgical procedures.

The criteria by which a slide was considered as suggestive of maliganacy corresponded in general to those outlined by Papanicolaou and Traut. Emphasis was placed on abnormalities in size, morphology, and staining reaction of the nuclei. Bizarre morphology and size of the cell, abnormalities in the staining reaction, and character of the cytoplasm were considered suspicious and warranted more intensive search for abnormal cells, but a diagnosis of malignancy was not made on the latter criteria alone. The presence of red cells, histiocytes, giant cells, and increased numbers of leucocytes were almost always found in positive smears, so that their mere presence was regarded with suspicion, but these same cells may be found in benign conditions, particularly those eliciting an inflammatory response.

Each slide was marked by a number and was so reported, so that the patient and the clinical history were entirely unknown to the reader of the slides. On the other hand, the pathologic diagnosis of removed tissue was submitted by the pathologist (Dr. J. Hoffman) without any knowledge on his part of the findings of the cytologist (Dr. A. E. Rakoff). In instances where no gynecologic operative procedure was carried out, the diagnosis was established clinically. The study was continued until 500 consecutive cases had been completed.

Results

Among the 500 consecutive gynecologic patients in this study, sixty-three patients had cancer of the uterus proved by histologic examination of tissue removed by biopsy or at operation (Table I). There were fifty-seven

*These stains were generously furnished through the courtesy of the Ortho Research Foundation, Raritan, New Jersey. At present we are also using stain EA 50, which gives excellent cytologic detail.

patients with squamous-cell carcinoma of the cervix, five patients with adenocarcinoma of the endometrium, and one patient with a fibrosarcoma of the uterine fundus. Of the 437 patients who were classified as negative for uterine cancer, approximately two-thirds had various operative procedures which provided tissue for histologic examination. The remaining patients had various gynecologic or related conditions in which operation was not necessary for diagnosis or treatment.

TABLE I. FINAL DIAGNOSIS IN PATIENTS STUDIED

Total No. of Patients			500
Patients with Uterine Cancer			63 or 12.6%
Cervical:	Squamous cell	57 or 90.5%	
	Adenocarcinoma	0	
Fundal:	Adenocarcinoma	5 or 7.8%	
	Fibrosarcoma	1 or 1.8%	

The findings of the vaginal cytology smears with respect to cells suggesting uterine cancer are summarized in Table II. For the entire group the smear gave a correct correlation in 94.8 per cent of the cases. It will be noted at once, however, that correct results were far better for the large group of patients who did not have cancer than for the smaller group who did have a uterine malignancy (Tables III and IV). False positives occurred in seven, or only 1.6 per cent of the 437 negative patients, while the diagnosis was missed in nineteen, or 30 per cent of the sixty-three positive cases.

TABLE II. RESULTS OF SMEARS FOR ENTIRE GROUP (500 PATIENTS)

	NO.		PER CENT
Correct results	474	or	94.8
Correct positive	44		
Correct negative	430		
Incorrect results	26	or	5.2
False positive	7		
False negative	19		

TABLE III. RESULTS OF SMEARS IN CANCER PATIENTS

	ENTIRE GROUP	CERVICAL CANCER	FUNDAL CANCER*
NO. OF PATIENTS	63	57	6
Correct positive smears	44 or 70.0%	40 or 70.2%	4 or 66.7%
False negative smears	19 or 30.0%	17 or 28.8 %	2 or 33.3 %

*Including one case of fibrosarcoma, diagnosed on smears as "malignant, probably cervical."

TABLE IV. RESULTS OF SMEARS IN NEGATIVE PATIENTS

No. of patients	437
Correct negative smears	430 or 98.4%
False positive smears	7 or 1.6%

There were but five patients with fundal carcinoma. In two of the cases the vaginal smear was reported as negative. There was one case of fibrosarcoma of the uterus, which was correctly reported as positive for uterine malignancy; however in this instance, the type of malignancy was questionable on the basis of the smear, and was finally incorrectly reported as cervical in origin. The abnormal cells noted on the smear were of the elongated spindle variety. The fifty-seven cases of cervical carcinoma were all of the squamous type. A diagnosis of squamous cell carcinoma of the cervix was made by the vaginal smear in forty, or 70.2 per cent of the cases, and missed in seventeen, or 28.8 per cent.

Review of the slides in which the diagnosis of squamous cell carcinoma had been missed showed the presence of normal cervical cells in all cases. In most of the slides in this group, the cervical cells were present in increased number, and in a high percentage there were also many red cells, histiocytes and an increased number of leucocytes. In three of the cases cervical cells were seen which were considered bizarre but not thought to be of the malignant type. These smears would ordinarily have been classified as doubtful and would have been repeated but for the specific nature of this study. In the remaining 14 cases, however, no real suspicion of malignancy was excited.

The two cases of fundal carcinoma which were missed cytologically showed increased numbers of endometrial cells with evidence of bleeding and inflammation as well. However, the cells did not present more than a normal variation in size, nor did the nuclei exhibit abnormal morphology or unusual hyperchromatic staining.

The final diagnoses based on pathologic and/or clinical findings in patients in whom the smears were incorrectly classified as positive are given in Table V.

Discussion

It is the opinion of those who have worked most with the vaginal cytology smear for the diagnosis of uterine cancer that this procedure has real merit. However the most enthusiastic workers in this field acknowledge that there are definite limitations in its application and usefulness. The warning has been stressed repeatedly that the vaginal cytology smear is not intended to replace biopsy of the cervix or diagnostic curettage of the fundus as the sole criterion for diagnosis and treatment. Even in the most competent hands it is freely acknowledged that some cases of carcinoma will be missed by the vaginal smear method and on occasion an apparent diagnosis of carcinoma will be suggested by the vaginal smear in patients subsequently proved to have nonmalignant lesions. The statistical accuracy of the procedure has been reported upon by several groups of workers. Papanicolaou and Traut[2] failed to detect malignant cells in the vaginal smears of patients with demonstrable carcinoma of the cervix in only four of 127 patients, and failed to diagnose carcinoma of the fundus in seven of fifty-three patients with this condition, thus giving an incidence of false negative smears for the cervical cases of 3.2 per cent, and for the fundal cases of 9.3 per cent. In 1945 Meigs[3] reported a series of 1,015 cases with an over-all error of 4 per cent. In a more recent review of 1,875 cases studied in the laboratory of the Vincent Memorial (Massachusetts General) Hospital, Fremont-Smith and Graham[5] found the procedure to have an over-all diagnostic accuracy of over 96 per cent. However, further scrutiny of their statistics shows that the percentage error in patients with proved carcinoma is considerably higher than in the negative cases. Thus, an incorrect negative diagnosis was made in 10.3 per cent of 154 carcinoma cases, while false positives were reported in 2.9 per cent of 861 negative cases, although the over-all total diagnostic error was but 4 per cent. It is apparent that the latter figure was much influenced by the high proportion of negative cases. Ayre,[7] in a study of 580 cases, reported missed diagnoses amounting to 6 per cent in 100 patients who had a positive tissue diagnosis of malignancy. False positive smears however, occurred in only nine patients, or 1.9 per cent of the 475 who were negative for carcinoma.

Jones and her co-workers[6] had an error of 11 per cent in false positives and 9 per cent in false negatives in a group of 432 cases, in eighty-two of which a final diagnosis of malignancy was established.

TABLE V. PATIENTS WITH FALSE POSITIVE SMEARS

FINAL DIAGNOSIS	VAGINAL SMEAR
Age 52 years 1. Hyperplastic endometrium Fibromyomata	Squamous cell carcinoma
Age 44 years 2. Functional uterine bleeding	Endometrial carcinoma
Age 22 years 3. Pelvic inflammatory disease	Squamous cell carcinoma
Age 28 years 4. Pelvic inflammatory disease	Squamous cell carcinoma
Age 18 years 5. Pelvic inflammatory disease	Squamous cell carcinoma
Age 24 years 6. Abortion induced?	Endometrial carcinoma
Age 55 years 7. Cervical polyp benign	Squamous cell carcinoma

It will be note that these statistics, including those reported in the present study, show a considerable degree of variation. This may be attributed to a number of factors inherent in the technique, which may be most conveniently summarized under the following headings:

(1) *Collection of Vaginal Smears.*—There has been considerable discussion as to whether smears should be collected from the posterior fornix of the vagina as originally advocated by Papanicolaou or from the cervix as advocated by Ayre and his associates.[8] Endocervical and endometrial smears also were suggested by Papanicolaou[9] as a further diagnostic aid in selected cases. It has been pointed out that the posterior fornix is the natural collecting place for exfoliated cells from every portion of the genital tract and that material collected from this source is most likely to be representative of all portions. On the other hand, if a lesion is visible or accessible, material collected from such a source is most likely to contain a higher proportion of abnormal cells. The percentage of endometrial cells has been claimed to be higher in the cervical secretion than in the vaginal smear. Although the present study was limited to smears taken only from the vagina, other observations which we have made lead us to believe that for routine purposes smears taken from both sources are probably better. We have noted occasional instances in which vaginal smears failed to show abnormal cells although the latter were found in smears prepared from the cervix. Nevertheless, cervical smears alone have not proved generally to be more accurate, in our experience, than those from the vaginal source alone. It has been our recent practice, therefore, to collect both cervical and vaginal smears wherever possible.

(2) *The Number of Smears Examined.*—Unquestionably the larger the number of samplings taken from a patient, the more accurate the results. This factor is an important one and probably explains the remarkable statistics reported by Papanicolaou and Traut,[2] since they state that many smears were taken from the patients they studied. Unfortunately, this has a certain practical limitation, since if the smear is completely negative and the patient presents no suspicious symptoms or lesions, there would be little reason for repeating smears. It was with this thought in mind that the present study was limited to a single set of smears, and it is our opinion that the high percentage of positive cases missed can be attributed chiefly to this factor. It

has been our policy, since the completion of this study, that whenever large numbers of cervical or endometrial cells are found which are at all bizarre to ask for repeated smears. Not infrequently much repetition has been rewarded by eventually finding cells suggestive of malignancy. On the other hand, it has been pointed out in the results presented that there have been numerous instances in which the initial smear failed to arouse sufficient suspicion to warrant further investigation. This we regard as the chief danger of the vaginal cytologic method, namely, the false security that a negative report may engender, particularly among those who do not appreciate its limitations.

(3) *The Personal Factor.*—There can be no question that the successful use of the vaginal smear method, even in the hands of competent microscopists, depends largely upon a wide experience in interpreting the cells which may be found on the smears. A large variety of cells which normally may be found in the vagina arise from all parts of the genital tract, and variations due to age, alterations in ovarian activity, functional disturbances, inflammatory reactions, and various benign growths, make it most difficult to evaluate cells regarded as suspicious of malignancy. In analyzing the statistics from different clinics it is quite apparent that the personal factor has been an important one, since some groups have a considerable error in false positives while in others the percentage of false negatives has been greater. Our own practice has been to adopt a rather rigid standard in reporting smears suspicious of malignancy and to indicate other smears containing cells not fully meeting these requirements as "doubtful." Much can be said on both sides of this question. If the diagnostic criteria are made too rigid it is quite possible that positive cases will be overlooked. On the other hand, if smears are reported positive on an insecure basis, unnecessary biopsies or even operations may be performed. Even with our most rigid standards we have had several instances in which biopsy or operation failed to reveal a malignant lesion; yet these have been more than compensated for with several cases in which operation was performed on the basis of a vaginal smear alone and in which carcinoma was found. One such case proved to be a myosarcoma of the tube and in another instance an endometrial carcinoma was discovered in patients not included in this study.

A point not to be overlooked in a study of this kind is the value of the vaginal smear in furnishing information concerning the patient other than the presence of malignant cells. The usefulness of the cytologic smear of determining ovarian function is now well established. Although the cytologic findings in pregnancy are not absolutely characteristic the experienced observer soon learns to detect cells suggesting this possibility in a fairly high percentage of the cases. If in addition one finds evidences of bleeding, plus the presence of decidual cells or even cells from the trophoblast, the diagnosis of threatened abortion is frequently suggested. The vaginal smear picture in cervical infections is also often quite characteristic, being evidenced by large numbers of cells from the exocervix and from the endocervix, much mucus and large numbers of leucocytes. Trichomonads and fungi can quite readily be detected on these smears, even though the stains used are not ideal for their demonstration. Pelvic inflammatory disease often presents a vaginal smear most difficult of evaluation and in some instances the cells present are not only bizarre but sometimes suggestive of malignancy. In the present study as well as in our general experience, pelvic inflammatory disease is more likely to be responsible for a false positive smear than any other type of lesion. Cervical polyps present a problem also in that large numbers of cervical cells are present, often of bizarre shape, but usually with fairly normal looking nuclei. These are but a few of the problem pictures which the vaginal cytology smear may present.

In conclusion, the present study corroborates the general value of the vaginal smear technique as a useful procedure for the routine study of gynecologic patients, and for the routine study prescribed in Health Maintenance and Cancer Prevention-Detection Clinics. In other words, it offers a measure of further investigation in those patients presenting no abnormal symptomatology and no visible or palpable evidence of a lesion suspicious of malignancy. In this respect, if carefully and cautiously used, the vaginal smear technique may well take its place as a routine public health diagnostic measure. The results emphasize however, that reliance cannot be placed on a single set of smears for the detection of uterine malignancy, since a high percentage of cases will be missed. It emphasizes the importance of fully investigating every case which presents cells suggestive of malignancy, since the percentage of false positives is not high. If intelligently used as an adjunct to other well-recognized procedures, particularly biopsy and curettage, the vaginal smear may be employed with benefit not only for the detection of cancer but in obtaining useful information concerning the functional state of the ovaries, the presence of inflammatory lesions and benign tumors of the genital tract. If employed overenthusiastically without regard to its limitations, and the use of the vaginal smear technique may lead to failure to employ more absolute methods of diagnosis or indiscriminate surgery.

Summary

1. Vaginal smears for cytologic study were collected on 500 consecutive patients admitted to the gynecologic ward. The vaginal smears were read by number and later compared with the pathologic and clinical findings.

2. Sixty-three patients had proved uterine carcinomas, fifty-seven being squamous-cell carcinomas of the cervix, five were adenocarcinomas of the endometrium and there was one fibrosarcoma. The vaginal findings afforded correct correlation in 474, or 94.8 per cent of the 500 patients, forty-four being correct positives and 430 correct negatives. Incorrect results were obtained in twenty-six or 5.2 per cent of the cases, seven being false positives, and nineteen being false negatives.

3. In the sixty-three cancer patients, correct positive smears were obtained in forty-four, or 70.0 per cent. Negative smears were obtained in nineteen, or 30.0 per cent. In the fifty-seven cases of cervical cancer seventeen, or 28.8 per cent, were missed, while in the six patients with fundal cancer two, or 33.3 per cent, were not detected.

4. Excellent correlation was obtained in the 437 patients who did not have carcinomas; correct negative smears were obtained in 430, or 98.4 per cent, while false positives occurred in only seven, or 1.6 per cent. It is emphasized that the good over-all correlation of 94.8 per cent was largely influenced by the high proportion of negative patients and it is pointed out that this factor has influenced the results in some of the earlier studies by other workers.

5. The factors influencing the accuracy of the cytologic method for the diagnosis of uterine cancer are discussed. It is contended that smears taken from the vagina and the cervix are preferable to those from either source alone. The advantages of repeated samplings are emphasized by the high percentage of missed positive cases on a single sampling. The influence of the personal factor in the interpretation of atypical slides is pointed out.

6. The value of the vaginal smear as a routine procedure on the gynecologic service is indicated as a diagnostic aid not only in the detection of uterine cancer but in affording information concerning the functional status of the patient and infections of the genital tract.

7. The necessity for recognizing the limitations of the cytologic method is emphasized since its indiscriminate use may lead to failure of employing more absolute methods of diagnosis or indiscriminate surgery.

References

1. Papanicolaou, G. N.: Proc. of the Third Race Betterment Conference, 1928, P. 528.
2. Papanicolaou, G. N., and Traut, H. P.: Diagnosis of Uterine Cancer by the Vaginal Smear, New York, 1943, The Commonwealth Fund.
3. Meigs, J. V., Graham, R. M., Fremont-Smith, M., Kapnick, I., and Rawson, R. W.: Surg., Gynec. & Obst. **77**: 449, 1943.
4. Fremont-Smith, M., Graham, R. M., Jansen, L. T., and Meigs, J. V.: J. Clin. Endocrinol. **5**: 40, 1945.
5. Fremont-Smith, M., and Graham, R. M.: Progress in Gynecology, P. 92, Edited by Meigs, J. V., and Sturgis, S. H.: New York, 1947, Grune & Stratton.
6. Jones, C. A., Neustaedter, T., and Mackenzie, L. L.: Am. J. Obst. & Gynec. **49**: 159, 1945.
7. Ayre, J. E.: Am. J. Obst. & Gynec. **51**: 743, 1946.
8. Ayre, J. E.: Bauld, W. A. G., and Kearns, P. J.: Am. J. Obst. & Gynec. **50**: 102, 1945.
9. Papanicolaou, G. N.: Am. J. Obst. & Gynfc. **51**: 316, 1946.

OBSERVATIONS ON VAGINAL ABSORPTION OF PENICILLIN*

STUART ABEL, M.D., CHESTER J. FARMER, M.A., AND JEANNE DOUCETTE, B.S.,
CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology and Chemistry, Northwestern University Medical School)

DURING a recent investigation of the value of penicillin vaginal suppositories in the treatment of vaginitis, concomitant observations were made relative to blood penicillin levels in the patients treated. Some interesting, if somewhat variable levels were obtained indicating inconsistent vaginal absorption in this group of patients with vaginitis. It seemed propitious to further our knowledge of the rate and degree of absorption of penicillin calcium from the vagina in a control group. Such a control group was organized from among our young single hospital nurses. Subjects in whom blood level studies were conducted were divided into four small groups as follows:

Group I is composed of ten patients from among the cases treated for vaginitis. The accompanying tables include the essential relevant data. One suppository containing 100,000 units of penicillin was inserted vaginally prior to the blood level studies in each patient.

Group II includes five additional patients with vaginitis in whom studies were made subsequent to the insertion of two suppositories (200,000 units). Table II follows.

Group III represents five hospital clinic patients selected at random for similar penicillin blood level studies following vaginal insertion of 200,000 units of penicillin. These five subjects were free of vaginal pathology. The pertinent detail in each case is included in Table III.

And finally, group IV is composed of nineteen of our single hospital nurses. These girls were contacted individually and told in detail of the proposed study. All were normal young menstruating women free of gynecologic pathology. Four studies were made in each volunteer at different stages during a menstrual cycle beginning at the completion of a period and ending just prior to the onset of the subsequent period. The blood levels in each instance again were determined following the vaginal insertion of two penicillin suppositories (200,000 units). During the ensuing four hours while the study was in progress, the girls were instructed to remain quietly in bed. Again the accompanying table includes the pertinent data.

The average blood levels for groups I, II and III are represented in the following graph. As seen in Table IV, the few levels obtained in group IV were so low as to be unassayable by the method used. Graphic representation of the results in group IV is not possible.

*Vaginal suppositories were generously supplied by the Schenley Corporation, New York.

TABLE I. (100,000 UNITS PENICILLIN)

NAME	AGE	MENSTRUAL HISTORY	VAGINAL EXAMINATION	VAGINAL SECRETIONS	VAGINAL CULTURE	BLOOD LEVELS ½ HR.	1 HR.	2 HR.	3 HR.	DATE
A. K.	56	Postmenopausal LMP 1939	Senile vaginal mucosa with vaginitis	Not reported	Not reported	1.0	1.0	.50	.25	7/ 5/46
M. D.	48	Postmenopausal LMP 1930	Senile vaginal mucosa with vaginitis	Few WBC Few bacteria	Diphtheroids; *B. Coli*	1.0	.50	0.0	0.0	8/23/46
E. M.	41	LMP March, 1944	Recent vaginal plastic operation; marked vaginitis	Many WBC Rare RBC Many bacteria	*Staph. albus*, nonhemolytic Alpha hemolytic streptococcus	0	0	0	0	7/15/46
R. K.	30	Cycle 28/5 LMP 7/10/46	Endocervicitis; vaginitis with much leucorrhea	Moderate WBC Moderate bacteria Occ. RBC	Nonhemolytic *Staph. albus*	.125	.125	.06	.03	7/15/46
E. L.	59	Postmenopausal LMP 1937	Senile vaginal mucosa with severe vaginitis and profuse leucorrhea	Many bacteria Many WBC	Nonhemolytic streptococcus	0.0	.06	.05	.06	7/10/46
M. K.	26	Cycle 28/4 LMP 6/28/46	Marked vaginitis	Many WBC Mod. bacteria Occ. tricho.	Nonhemolytic *Staph. albus* Hemolytic *Staph. albus* Nonhemolytic streptococcus	.03	.03	0	0	7/15/46
V. P.	28	Cycle 28-32/5 LMP 6/5/46	Endocervicitis; vaginitis with much leucorrhea	Many WBC Many bacteria	Diphtheroids	.12	.50	.50	.50	8/12/46
M. D.	25	Cycle 28/5 LMP 7/7/46	Severe vaginitis	Many WBC Many bacteria	Diphtheroids	.125	1.0	.25	.03	7/22/46
E. L.	53	Postmenopausal LMP 1941	Senile vaginal mucosa with vaginitis	Many WBC Many RBC Many bacteria	Nonhemolytic *Staph. albus; B. Coli*	4.0	1.0	.25	.06	7/ 3/46
A. T.	23	Cycle 28/6 LMP 9/19/46	Marked vaginitis with leucorrhea; typical trichomonas	Many WBC Many bacteria Many tricho.	Moderate gamma streptococcus and diphtheroids	.25	.50	.125	.06	7/15/46

Am. J. Obst. & Gynec. March, 1948

TABLE II. (200,000 UNITS PENICILLIN)

NAME	AGE	MENSTRUAL HISTORY	VAGINAL EXAMINATION	VAGINAL SECRETIONS	VAGINAL CULTURE	BLOOD LEVELS ½ HR.	1 HR.	2 HR.	3 HR.	DATE
C. W.	34	Cycle 28/5 LMP 7/22/46	Severe vaginitis; typical tricho.	Many WBC Many bacteria Many tricho.	Diphtheroids Micrococcus Alpha streptococcus	0.0	0.0	.125	0.0	7/30/46
C. B.	59	Postmenopausal LMP 1941	Senile vaginal mucosa with vaginitis	Many WBC Many bacteria	Diphtheroids Alpha streptococcus	0.0	0.0	0.0	0.0	7/30/47
J. F.	23	Cycle 21/8 LMP 6/8/46	Endocervicitis and vaginitis	Many WBC Many bacteria	Diphtheroids *Staph. albus*	0.0	.25	1.0	2.0	10/23/47
E. L.	59	Postmenopausal LMP 1937	Senile vaginal mucosa with vaginitis and severe leucorrhea	Many WBC Many bacteria	Nonhemolytic streptococcus	2.0	1.0	.125	0.0	11/15/46
L. C.	31	Abd. complete hysterectomy in April, 1946; both ovaries left in	Vaginitis	Many WBC Many bacteria	Alpha streptococcus *B. Subtilis*	0.0	.25	.25	.25	8/13/46

TABLE III. (200,000 UNITS PENICILLIN)

NAME	AGE	MENSTRUAL HISTORY	GYNECOLOGIC PATHOLOGY	BLOOD LEVELS ½ HR.	1 HR.	2 HR.	3 HR.
B. V.	39	LMP just prior to test—periods irregular	Had vaginal plastic No pathology now Vagina clean (intermenstrual spotting)	0.0	0.0	0.0	0.0
S. R.	46	Cycle 21-28/10 LMP 11/9 Test 11/19	No pathology (menorrhagia) Vagina clean	0.0	0.0	0.0	0.0
N. D.	51	LMP 23 years ago following abdominal section	Large cysto- and rectocele Cervix and part of corpus seemed present (no vaginal pathology)	1.0	2.0	1.0	0.50
M. R.	60	LMP 19 years ago	No gynecologic pathology Vagina clean (Vaginal spotting?)	0.0	0.50	0.50	0.50
H. L.	43	Cycle 28/5 LMP 3 weeks prior to test	Cystocele and rectocele Vagina clean	0.0	0.25	1.0	0.25

The method of assay employed for this work was the Fleming-Wright slide cell technique as described by Heilman and Herrill[1] with the omission of dilution transfer to the slides. Defibrinated rabbit blood containing a beta hemolytic streptococcus sensitive to penicillin (culture C203) was added to the serial dilutions of the serums and incubated overnight. On the following day the assay was observed for presence or absence of hemolysis. The last tube of the serial dilution containing blood serum showing no hemolysis was taken as the end point and its contents of penicillin was considered identical to that of a standard prepared similarly containing a known amount of penicillin.

Discussion

From the results obtained one is impressed with the extreme variability of blood penicillin levels following insertion of penicillin vaginal suppositories. It is interesting to note the marked differences in levels obtained among individual patients within the same group. The lack of appreciable levels in the well-controlled group of nurses is particularly striking. A short comment relative to the few recent articles dealing with vaginal absorption of penicillin seems appropriate before attempting to evaluate our own results.

Lovelady, Randall, and Hosfeld[2] reported blood penicillin levels in thirty-six postpartum patients following the insertion of vaginal suppositories. These patients were confined to bed. No mention is made of the elapsed time since the patients were delivered. The thirty-six patients were divided into three groups of one dozen each. In the first group one suppository was used (100,000 units penicillin), in the second group two suppositories were used, and in the third group three suppositories were used. Levels were determined at three and five hours by the slide-cell technique of Heilman. In group one, five patients showed a low blood level after three hours and seven did not. There were no levels at five hours. Six of the patients in group II showed a somewhat higher level at three hours and in two of these there was still an appreciable level at five hours. In group III all but three of the twelve patients showed levels at three hours,

one as high as 0.5 units per c.c. serum. Appreciable levels were maintained in seven of these patients for 5 hours. From their results the Mayo group advocated the use of the suppositories as a routine measure in the preparation of patients for delivery and perhaps in preparation for Cesarean section or hysterectomy. There is no evidence that absorption from the postpartum vagina necessarily indicates absorption in other conditions.

Rock, Barker, and Bacon[3] reported from Harvard Medical School on their experiences with the vaginal absorption of penicillin. They concluded that except during the last two months of pregnancy, penicillin is easily absorbed from cocoa butter suppositories in the vagina, giving therapeutic blood levels for from four to six hours. These conclusions were based on nine nonpregnant patients with vaginitis or cervicitis and four patients who were awaiting delivery. Seven recently delivered postpartum patients comprising a third group also showed good blood levels.

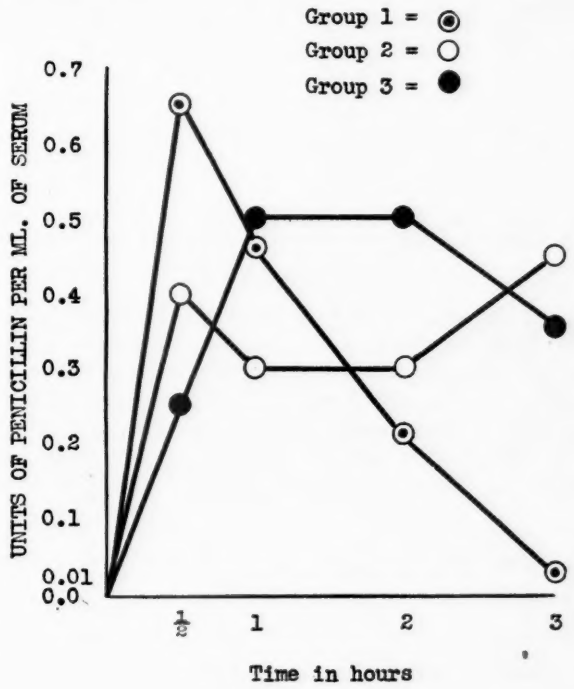


Fig. 1.

Goldberger, Walter, and Lapid[4] concluded that penicillin in the form of suppositories is readily absorbed through the vagina and that therapeutic levels are easily attained and maintained for at least three hours. These workers used 500,000 units of penicillin. Their average blood penicillin levels at the end of one-half, one, two, and three hours were 0.38 units, 1.35 units, 0.96 units, and 0.38 units respectively. Studies were conducted in ten patients, seven of whom were normal menstruating women. Two were postmenopausal and one was amenorrheic with virilism. All were free of vaginal pathology. Vaginal pH studies were made prior and subsequent to the tests. On studying the table of results, no correlation of the age, menstrual cycle, or the vaginal pH with the levels obtained is apparent. The authors conclude that the vaginal route may be the method of choice for the administration of penicillin in the adult female.

TABLE IV. (200,000 UNITS PENICILLIN)

NAME	AGE	MENSTRUAL HISTORY	DAY OF CYCLE	BLOOD LEVELS			
				½ HR.	1 HR.	2 HR.	3 HR.
A. A.	22	Cycle 28/7	1/ 6/47	0	0	0	0
		LMP 1/1/47	1/13/47	0	0	0	0
			1/20/47	0	0	0	0
			1/23/47	0	0	0	IC
A. H.	26	Cycle 28-30/4	1/ 6/47	0	0	0	0
		LMP 1/2/47	1/14/47	0	0	0	0
			1/21/47	0	0	0	0
			1/29/47	0	0	0	0
M. K.	26	Cycle 30/7-8	1/ 6/47	0	0	0	0
		LMP 12/29/46	1/13/47	0	0	0	0
			1/20/47	0	0	0	0
			1/27/47	0	0	0	0
D. O.	24	Cycle 28/4	1/ 7/47	0	0	0	0
		LMP 1/3/47	1/15/47	0	0	0	0
			1/23/47	IC	0	0	0
C. U.	25	Cycle 21/5	1/ 9/47	0	0	0	0
		LMP 1/5/47	1/14/47	0	0	0	0
			1/21/47	0	0	IC	0
			1/25/47	0	0	0	0
S. H.	27	Cycle 22/7	1/13/47	0	0	0	0
		LMP 1/7/47	1/20/47	0	0	0	0
			1/27/47	0	0	0	0
			2/ 2/47	0	0	0	0
W. F.	24	Cycle 30/5	1/11/47	0	0	0	0
		LMP 1/7/47	1/20/47	0	0	0	0
			1/28/47	IC	IC	0	0
			2/ 6/47	0	0	0	0
A. G.	26	Cycle 28/4	2/ 3/47	0	0	0	0
		LMP 1/29/47	2/10/47	0	0	0	0
			2/17/47	0	0	0	0
			2/24/47	0	0	0	0
A. H.	25	Cycle 30/5	1/ 9/47	0	0	0	0
		LMP 1/5/47	1/17/47	0	0	0	0
			1/27/47	0	0	IC	0
			2/ 3/47	0	0	0	0
R. W.	23	Cycle 28/5	1/18/47	0	0	0	0
		LMP 1/13/47	1/27/47	0	0	0	0
			2/ 2/47	0	0	0	IC
			2/ 8/47	0	0	0	0
C. C.	22	Cycle 28/5	1/18/47	0	0	0	0
		LMP 1/12/47	1/25/47	0	0	0	0
			2/ 1/47	0	0	0	0
			2/ 8/47	0	IC	IC	0
J. B.	25	Cycle 28/4-5	1/20/47	0	0	0	0
		LMP 1/15/47	1/28/47	0	0	0	0
			2/ 5/47	0	0	0	0
			2/13/47	0	0	0	0
C. C.	23	Cycle 25/5	1/14/47	0	0	0	0
		LMP 1/10/47	1/21/47	0	0	0	0
			1/28/47	0	IC	0	0
			2/ 4/47	0	0	0	0
E. A.	26	Cycle 28/4-5	1/14/47	0	0	0	0
		LMP 1/9/47	1/21/47	0	0	0	0
			1/28/47	0	0	0	0
			2/ 6/47	0	0	0	0

TABLE IV—CONT'D

NAME	AGE	MENSTRUAL HISTORY	DAY OF CYCLE	BLOOD LEVELS ½ HR.	1 HR.	2 HR.	3 HR.
R. B.	29	Cycle 28/5	1/21/47	0	0	0	0
		LMP 1/16/47	1/29/47	0	0	0	0
			2/ 5/47	0	0	0	0
			2/12/47	0	0	0	0
C. G.	24	Cycle 28/5	1/ 7/47	0	0	0	0
		LMP 1/13/47	1/25/47	0	0	0	0
			2/ 1/48	0	0	IC	0
			2/ 8/48	0	IC	0	0
W. P.	22	Cycle 25/4	1/25/47	0	0	0	0
		LMP 1/22/47	2/ 1/47	0	0	0	0
			2/ 8/47	0	0	0	0
			2/15/47	0	0	0	0
A. D.	34	Cycle 28/4-5	1/20/47	0	0	0	0
		LMP 1/15/47	1/28/47	0	0	0	0
			2/ 4/47	0	0	0	0
			2/11/47	0	0	0	0
J. K.	23	Cycle 28-30/6	1/24/47	0	0	0	0
		LMP 1/20/47	2/ 3/47	0	0	0	0
			2/10/47	0	0	0	0
			2/17/47	0	0	0	0

IC—incomplete hemolysis which is interpreted to represent amounts so small that they were unassayable.

The most recent report is a paper by Schudmak and Hesseltine[5] of the University of Chicago. Their paper on "The Absorption of Penicillin from the Human Vagina" was read by title at a recent meeting of the Illinois section of the Society of Experimental Biology and Medicine. Although this paper is not available at the time of this writing, one of the authors has informed us through personal communication that vaginal absorption of penicillin as determined by their studies has been inconstant and unpredictable. This has certainly been our experience.

From the literature and from our own results it appears that there is some degree of vaginal absorption of penicillin under certain circumstances. However, the degree of absorption is extremely inconstant and unpredictable. A possible relationship of the vaginal pH and the degree of absorption occurred to us but Goldberger and his workers have not demonstrated any correlation. It seems feasible that the inflamed vaginal mucosa with the accompanying hyperemia incident to vaginitis might be conducive to a degree of absorption different from that of the normal vaginal mucosa in a healthy young patient. In the group of nineteen nurses, all subjects were at bed rest and loss of penicillin from the vagina was kept at a minimum. Tests were conducted by the same method and personnel as applied to our other three groups. The consistent lack of appreciable blood levels of penicillin in this group must be significant.

Goldberger's conclusion that vaginal administration of penicillin may be the method of choice in adult women seems unjustified in the light of our studies, if the production of therapeutic blood levels is the desired result. It

appears that such levels are not dependable following vaginal absorption of penicillin and that intramuscular administration is more feasible.

It is of importance to note that two of the nineteen nurses developed urticaria during the study and two of the patients with vaginitis and leucorrhea developed pruritus only after they had been on treatment some time and after the vaginitis and leucorrhea were much improved. Whether or not the pruritus was caused by the penicillin is problematical.

From our own experiences and those of others reporting recently, vaginal penicillin suppositories are of real value in the treatment of vaginitis. Such value probably stems from the local concentration rather than from the blood level obtained by absorption. The real value of vaginal penicillin suppositories is in the treatment of vaginitis, and the blood levels achieved during such therapy are incidental and of doubtful importance.

Conclusions

1. Penicillin, when administered in cocoa butter suppositories, is absorbed from the vagina under certain conditions.

2. The degree of absorption and the resulting blood penicillin level are subject to great variation and are difficult to predict in any given case. Apparently there is less absorption of penicillin from the normal vaginal mucosa than from the inflamed mucous membrane in a patient with vaginitis.

3. Because of the incidence of side reactions and, because of the unpredictable blood levels obtained subsequent to the use of penicillin vaginal suppositories, it does not seem rational to advocate this route of administration in preference to intramuscular injection or oral therapy when the desired result is the production and maintenance of a therapeutic blood penicillin level.

4. The real value of penicillin vaginal suppositories is in the treatment of vaginitis where the local concentration of penicillin is of prime importance and the production of blood levels is only a matter of secondary interest.

References

1. Heilman, D. H., and Herrell, W. E.: Am. J. Clin. Path. 15: 7-9, 1945.
2. Lovelady, S. B., Randall, L. M., and Hosfeld, S. M.: Proceedings of the Mayo Clinic, 21: 401, October 16, 1946.
3. Rock, John, Barker, R. H., and Bacon, W. B.: Science 105: 13, 1947.
4. Goldberger, M. A., Walter, R. I., and Lapid, L. S.: Am. J. Obst. & Gynec. 53: 529, 1947.
5. Schudmak, M., and Hesseltine, H. C.: Personal communication.

720 North Michigan Avenue.

THE PERMEABILITY OF THE HUMAN PLACENTA TO SODIUM IN NORMAL AND ABNORMAL PREGNANCIES AND THE SUPPLY OF SODIUM TO THE HUMAN FETUS AS DETERMINED WITH RADIOACTIVE SODIUM

L. B. Flexner, M.D., D. B. Cowie, Ph.D., L. M. Hellman, M.D., W. S. Wilde, Ph.D., and G. J. Vosburgh, M.D., Baltimore, Md.

(From the Department of Embryology, Carnegie Institution of Washington, Baltimore, Department of Terrestrial Magnetism, Carnegie Institution of Washington, Washington, and the Department of Obstetrics, Johns Hopkins University and Hospital)

TO OBTAIN comprehensive information on the permeability of the placenta, one should be in a position, ideally, to measure its permeability to many and diverse test substances. These substances should be closely related chemically and physically to those constituents of the maternal plasma which are normally transferred across the placenta from mother to fetus. The availability of radioactive and stable isotopes, together with exquisitely sensitive and reliable methods for their quantitative measurement, has furnished a method which satisfies this criterion. Because of the chemical identity of these isotopes with their naturally occurring counterparts in the body, we are assured that their biological behavior is normal when the precaution is taken of using radioactive substances in amounts substantially less than that known to produce radiation effects. A molecule may be identified or "marked" with an isotope (e.g., in "heavy water," hydrogen of atomic weight 2 replaces its isotope, hydrogen of mass 1, found in ordinary water) and the molecule subsequently traced by detecting the isotope. Or the isotope may be studied as an ion (e.g., Na^{24} which is radioactive and which is detected by one of several instruments used for measuring radioactivity).

The investigations to be reported here had as their objective the measurement of the permeability of the human placenta to sodium, primarily in normal cases, and, as occasion permitted, in the presence of disease. The observations have been made in twenty-seven women in whom pregnancy was terminated by abdominal hysterotomy before the period of viability or by cesarean section or pelvic delivery at or near term. Ten of these cases were presented in a preliminary report.[1] We entered upon this program with a background of studies on the placentas of animals representing each of Grosser's four morphological types[2]; we are able, consequently, to consider the results on man from the viewpoint of comparative physiology, and to relate them to the results obtained from other members of the hemochorial group. As in the animals studied, we shall also be interested, at various stages of pregnancy, in the amount of sodium supplied to the human fetus as this is related to the fetal need for sodium during growth.

Rationale and Methods

When a radioactive isotope is used in biological research it is mixed with a preponderant quantity of its naturally occurring, nonradioactive isotope; the radioactive substance is employed to tag or label the naturally occurring substance so that the latter may be distinguished from that already present in the body. Thus when radioactive sodium (Na^{24}, i.e., Na with an atomic weight of 24) is used to study the behavior of sodium (Na^{23}) intrinsic to the body, the Na^{24} is present in the sample in an infinitesimally small amount as the chloride together with a weighable amount of ordinary NaCl. The mixture of the two isotopes is referred to as tagged or labeled sodium, and will be designated by the symbol Na.* In practice, a sample of tagged sodium is weighed and the radioactivity measured in terms of the radiation or counts emitted per second; if the radioactivity of any part of the sample is subsequently known, it is then possible to calculate the corresponding weight of the tagged sodium which is present. We shall present our data in terms of tagged sodium; it will be evident that this refers to sodium (Na^{24} plus Na^{23}) introduced into the body and is not to be confused with the sodium intrinsic to the body. The quantities of tagged sodium used in our experiments were kept as small as were compatible with precise measurements of their radioactivity and were so minute in comparison to the normal sodium content of the body that they are properly called tracer quantities (see Table I).

The fundamental assumption in the use of a radioactive isotope to measure placental permeability is that the radioactive substance crosses the membrane precisely as does its naturally occurring isotope, and therefore, the two isotopes cross the placenta in the same proportion as is found in the fluid bathing it. In the case of the placenta this means that:

$$\frac{Na_{mp}}{Na^*_{mp}} = \frac{Na_f}{Na^*_f} \quad (1)$$

where Na_{mp} refers to the concentration of normally occurring sodium in the maternal plasma, Na^*_{mp} to the concentration of tagged sodium in the maternal plasma; and Na_f and Na^*_f are the quantities of the corresponding substances transferred to the fetus during the time of an experiment.

Our experimental data have as a first aim the evaluation of Na_f. This quantity divided by the weight of the placenta will be taken as a measure of placental permeability to sodium. Na_f can be calculated from equation (1) if the other three quantities are known. The concentration of sodium in human plasma, Na_{mp}, has been frequently determined, and has an average value of 3.3 mg. per 100 c.c. of plasma.[3] The evaluation of Na^*_{mp} is less direct. After injection of a solution of Na*Cl into a maternal vein the concentration of Na* in the plasma rapidly diminishes due to its passage into the extracellular fluid of the mother. Since the amount of labeled sodium transferred to the fetus is directly proportional to its concentration in the maternal plasma, only the average concentration in the maternal plasma during the period of transfer is suitable for substitution in the equation. Our first series of experiments, therefore, was designed to measure the rate of disappearance of labeled sodium after its intravenous injection; and from these data the average plasma concentration was obtained. The measure of the quantity of labeled sodium transferred to the fetus (Na^*_f), moreover, is valid for substitution in the equation only if none returns from fetus to mother during the period of observation. It is reasonable to assume that early after introduction of the tagged sodium into the maternal circulation, its concentration in fetal plasma remains so low compared to that of maternal plasma that only a negligible quantity returns from fetus to mother. This condition was taken to be satisfied in the guinea pig[4] when the concentration of the tagged

sodium in the fetus (referred to a unit concentration of tagged sodium in the maternal plasma) increased linearly with time. The period of linear exchange in the guinea pig lasts for from two to three hours after injection; the rate of accumulation in the fetus then decreases until equilibrium is reached at about eight hours. Because of experimental limitations we have not been able to determine the period of linear acquisition by the human fetus. To be as certain as possible about procedure, however, delivery of the fetuses has usually been made approximately thirty minutes after injection of the radioactive material. This procedure gave concentrations of labeled sodium in the fetus as related to unit concentration in the maternal plasma well below the ratio for linearity in the guinea pig.

The umbilical cord was clamped as soon as possible, usually within a minute, after incision of the uterus was begun. Immediately thereafter a sample of maternal blood was taken. The fetus and placenta were weighed, the latter being freed of its membranes, cord, and superficial blood. Nonviable fetuses were ashed as previously described[4]; blood samples were secured from viable fetuses one to three hours after delivery. This time interval was chosen to permit equilibration of plasma sodium with extracellular sodium. The radioactivity of the samples of maternal plasma, fetal ash, and of the fetal plasma was then measured and the quantity of tagged sodium present in these samples calculated from the radioactivity. The total quantity of tagged sodium in a viable fetus was calculated from the concentration found in the plasma and from the known volume of the extracellular space which has been found to average 43.5 per cent of the body weight.[5] The average value for the concentration of tagged sodium in maternal plasma was obtained as will be described below in the presentation of the disappearance curve of tagged sodium from plasma.

The labeled sodium was prepared in the 60-inch cyclotron of the Department of Terrestrial Magnetism, Carnegie Institution of Washington, by deuteron bombardment of metallic sodium. After bombardment, the sodium was dissolved in ethyl alcohol, and Na*Cl then precipitated with concentrated HCl. Finally an aqueous solution of Na*Cl was made using distilled water. Appropriate precautions were taken with respect to tonicity, neutrality and sterility of the solution. The amount of tagged sodium injected into an individual averaged about 30 mg. with an activity of 0.3 millicurie. The radioactivity of the samples was measured by a temperature controlled, pressure ionization chamber connected to a string electrometer[4]; these measurements were corrected for self-absorption of radiation by the sample and for the background of the instrument.

Results

The disappearance curve for Na in plasma after its intravenous injection.*— As has been pointed out, the calculation of the placental transfer rate for sodium depends upon an accurate estimation of the average maternal plasma concentration of Na* present during the period of transfer under observation. This entails the description of the change in concentration of Na* in maternal plasma from the time of its intravenous injection until the time of delivery of the fetus. Multiple sampling of maternal blood at the time of the transfer studies was avoided by establishing a time-concentration curve in advance (Fig. 1). This was accomplished by injecting a known quantity of Na* into each of three normal, pregnant women. The curve was standardized so that the average concentration for a given pregnant subject could be determined by measurement of the Na* concentration of a single plasma sample taken at a known time. This

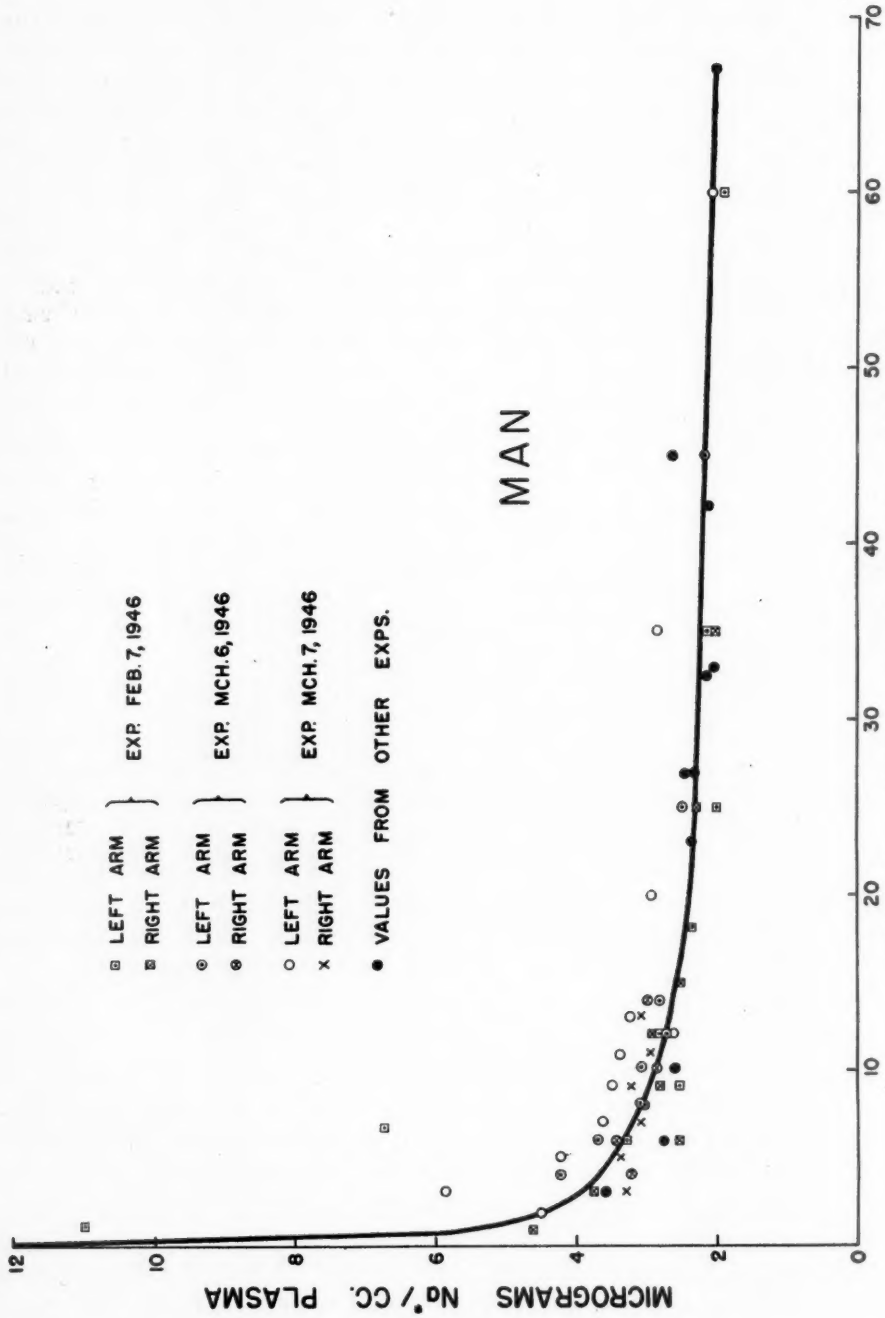


Fig. 1.—Change in concentration of Na^* in the plasma with respect to time. The points were adjusted to a standard basis by multiplying them all by a factor which brought the initial concentration to 12 micrograms per c.c. of plasma, as explained in the text.

was done as follows: For each of the three individuals studied we calculated the plasma concentration of Na* which could have been present immediately after injection if the injected Na* had been distributed uniformly in the plasma. A standard plasma volume of 45 c.c. per kilogram body weight was assumed. This initial concentration (which varied among the three subjects but averaged about 12 micrograms Na* per c.c. of plasma) in each woman was multiplied by whatever factor was necessary to convert it to a standard concentration of 12 micrograms Na* per cubic centimeter of plasma. Subsequent measurements of plasma concentration in each of the three cases were then multiplied by the same factor. Since the standard plasma volume which has been used as a constant, this treatment is equivalent to relating all concentrations to a constant quantity of Na* per unit body weight. The average concentration of Na* in the maternal plasma for a period of thirty minutes after injection was obtained from the standard curve of figure 1 as follows: The area under the curve from zero time to thirty minutes was measured with a planimeter. This area was then divided by the time interval, thirty minutes, to obtain the average altitude, or average concentration. The ratio of this concentration to that found at thirty minutes is the factor, 1.35, by which the concentration of Na* at thirty minutes in a subject must be multiplied to give the average concentration for that subject. Average maternal values calculated in this way are given in the last column of Table I.

As shown in Fig. 1, samples of blood were taken simultaneously from veins of the right and left arms. This provided a measure of mixing time and it was assumed that mixing was essentially complete when the amount of Na* in the two samples was about equal. In one subject, the mixing time estimated in this way amounted to about eight minutes; in the second, to twelve minutes; and in the third, to thirteen minutes. The average concentration of Na* in the maternal plasma will of course be affected by the mixing time. We believe that for our purpose the average concentration in the maternal blood of the placenta differs in no important way from that of the peripheral blood as we have established it.

The normal placental transfer rate for sodium at different gestational ages.—The amount of sodium transferred to a fetus during an experiment was calculated from equation 1. Values for Na^*_f and Na^*_{mp}, the latter averaged for the observed period of transfer, are given in Table I. Na_{mp} was taken to equal 3.3 mg. per c.c. The value of Na_f derived from these data was finally converted to milligrams of sodium transferred across one gram of placenta in one hour. The results are presented in Fig. 2.

The curve of Fig. 2 has been drawn to fit observations made on individuals in which there was no reason to suspect abnormality of placental function. Sixteen normal cases in this series were distributed among individuals who were delivered abdominally because of previous section, mental disease, chorea, tuberculosis, myoma of the uterus, pyelitis, or carcinoma of the abdomen. In addition there are two cases which have been observed during normal labor and vaginal delivery. Six of these cases fell within the ninth to seventeenth week of pregnancy; ten were between the thirty-sixth week and term; only three came between the seventeenth and the thirty-sixth week because of the rarity of interruption of pregnancy during this period.

TABLE I. VALUES FROM WHICH THE DATA OF FIG. 2 AND TABLE II HAVE BEEN DERIVED*

HISTORY NUMBER	INDICATION FOR OPERATION	DELIVERY TIME (MINUTES)	FETAL WEIGHT (GM.)	GESTATION AGE (WEEKS)	PLACENTAL WEIGHT (GM.)	Na* IN TOTAL FETUS (MICROGRAM)	Na*/C.C. OF MATERNAL PLASMA	
							FOUND (MICROGRAM)	AVERAGE (MICROGRAM)
103003	Previous section	33	2700	38	370	700	1.49	1.94
247063	Psychiatric	27	402	16	126	39.0	0.97	1.31
231656	Psychiatric	30	36	10	63	9.5	1.29	1.74
249863	Psychiatric	32	545	20	156	167	1.42	1.84
260095	Previous section	27	2180	37	214	668	4.43	5.98
	Twin pregnancy	28	2030		205	264	4.43	5.98
113669	Previous section	28	3040	40.	490	1230	2.67	3.60
128414	Pelvic delivery	55	3340	term	505	1120	1.34	1.60
376433	Previous section	33	3430	37	516	760	1.69	2.20
388120	Chorea	29	92	14	92	19.0	2.40	3.23
311276	Previous section	32	2100	34	370	835	1.79	2.34
254037	Pulmonary tbc.	30	4	9.5	19	0.61	0.88	1.18
386115	Pelvic delivery	30	3680	40	490	1240	1.60	2.16
136080	Myoma uterus	32	2790	36	490	1560	2.35	3.06
398157	Contracted pelvis	31	2630	36	375	1080	1.92	2.59
396381	Chr. pyelitis	46	1500	31	243	1120	3.00	3.80
406823	Ca. abdomen	30	152	17	97	67.0	2.86	3.86
408367	Contracted pelvis	30	2490	40	335	1190	3.86	5.22
257328	Epilepsy	35	19	12	34	10.5	3.58	4.65
240415	Chr. nephritis	31	14	12	34	30.4	4.33	5.84
165446	Hypertension	29	129	16	100	74.3	2.97	4.00
250383	Hypertension	27	614	24	168	49.0	0.45	0.61
259938	Hypertension	28	361	20	140	138	2.97	4.00
389368	Hypertension	31	2780	37.5	455	1190	2.24	3.02
247202	Pre-eclampsia	28	354	18	100	7.3	0.22	0.30
250393	Pre-eclampsia	31	1480	31	220	524	4.70	6.10
317603	Cardiac disease	29	247	18.5	121	278	2.00	5.20
376618	Cardiac disease	34	201	18	107	64.8	1.72	2.25

The average concentration of Na in the maternal plasma for the duration of the experiment has been calculated as explained in the text. Delivery time refers to the interval between i.v. injection of Na* and clamping of the umbilical cord.

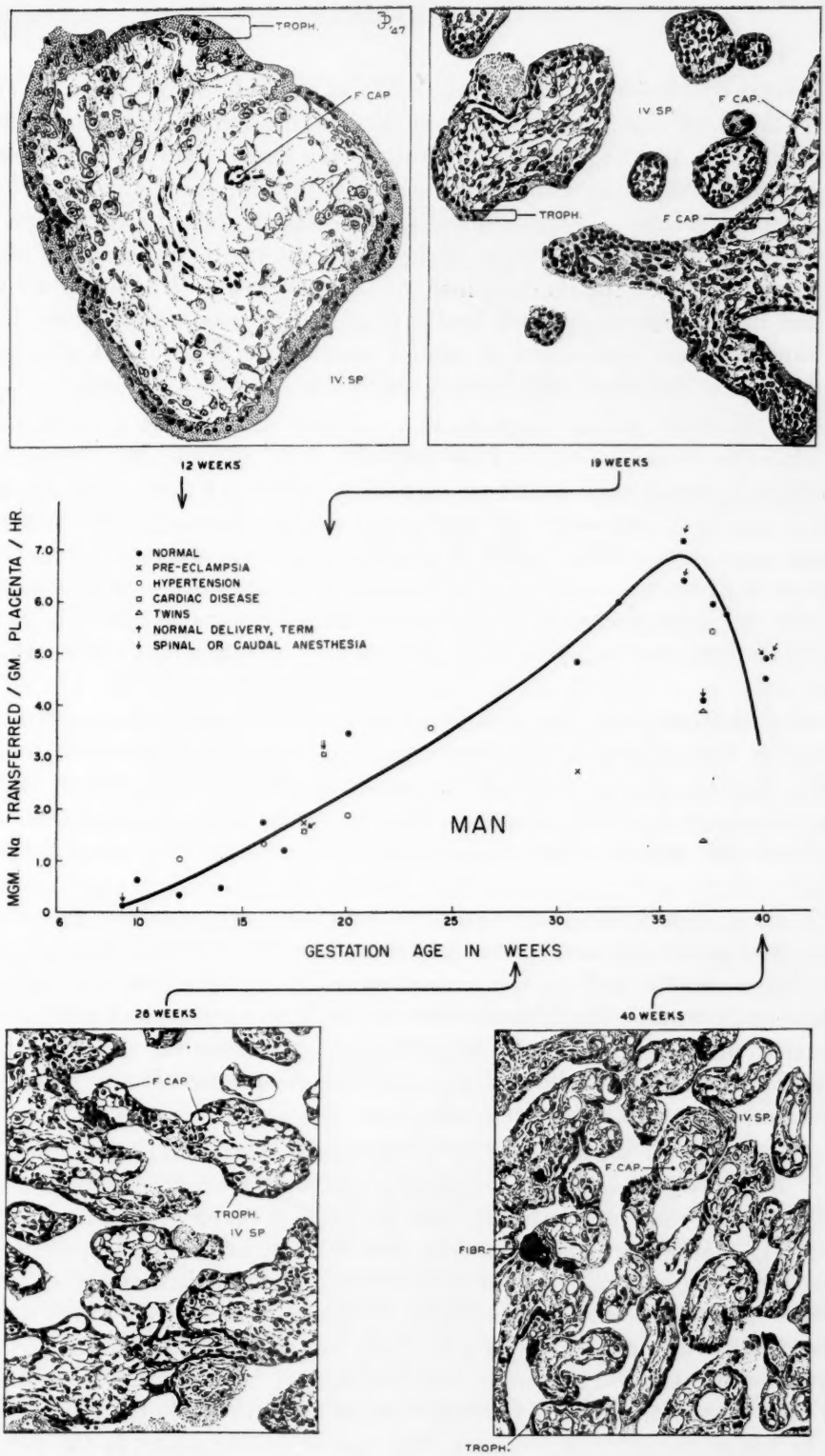


Fig. 2.—Variation of the rate of transfer of sodium with respect to gestation age. The points have been derived from the data of Table I. The camera lucida drawings (×155) are from sections of normal human placentas at the indicated gestational ages and illustrate the histological changes which can be correlated with the change in permeability. Note, as the placenta ages, decrease in thickness of trophoblast (Troph.), increase in surface of villi exposed to intervillous space (Iv. Sp.), and increase in number of fetal capillaries (F. Cap.). Fibr., fibrin.

Several conclusions of major interest to us are to be drawn from the results. The first is that the apparent permeability of the human placenta to sodium increases about 70 times from the ninth to the thirty-sixth week of gestation. The second is that from the thirty-sixth week to term there was in all but one case a rapid decrease in permeability; this decrease was most marked in a single case of twins. The third is that in the two cases where transfer was observed during normal labor for the half hour or hour preceding delivery, there was no decrease in transfer rate. And finally there was no evident difference between the transfer rates when spinal or caudal anesthesia was used and when general anesthesia was obtained with sodium pentothal or gas-oxygen-ether.

The effect of chronic hypertension, cardiac disease and pre-eclampsia on the placental transfer rate.—Five patients with chronic hypertension were studied, one complicated by chronic nephritis. Three of these were between the twelfth and twentieth weeks of pregnancy, one at the twenty-fourth week and the last near term. They varied in severity from mild degrees of hypertension with blood pressures of 140 to 150 over 90, to severe cases with retinal arteriosclerosis and hemorrhages and blood pressures of 180 over 110 or 120. As shown in Fig. 2, there was no evidence of abnormality of placental transfer in any of these cases.

Measurements were made on two patients with cardiac disease, both in the nineteenth week of pregnancy. In one there was complete heart block, diminished cardiac reserve and considerable vasomotor instability; in the other, rheumatic heart disease with mitral stenosis, a bundle branch block and moderate diminution in cardiac reserve. Both of these individuals had normal placental transfer rates.

Finally, observations were made on two cases of pre-eclampsia. One at a gestational age of eighteen weeks had severe hypertension and albuminuria with retinal hemorrhage and partial retinal detachment. The transfer rate in this patient was normal. The other woman, in the thirty-first week of pregnancy, had edema in addition to severe hypertension and albuminuria. The transfer rate in this case was reduced about 50 per cent; this is the single instance in our series where there has been a definite alteration.

Fetal need for sodium relative to its supply across the placenta.—The ratio of the quantity of a substance supplied to the fetus from the maternal plasma to the amount of that substance retained by the fetus in its growth has been called the safety factor for that substance.[4] The quantity of sodium transferred to the fetus across the placenta per hour is calculated from equation (1) as explained above. The amount of sodium retained by the fetus in an hour's growth is equal to the fetal weight multiplied by the hourly per cent weight increase of the fetus multiplied by the total sodium in a unit weight of fetal tissue. The safety factor has been calculated for four fetal ages and is given in Table II. The value of the safety factor varies from 160 at a fetal age of twelve weeks to the remarkably high value of 1130 at forty weeks. This means that of 1,130 parts of sodium delivered to the fetal circulation at forty weeks only one part is retained by the fetus in its growth, and 1,129 parts are returned to the maternal circulation.

TABLE II. FETAL NEED FOR SODIUM RELATIVE TO SODIUM SUPPLIED ACROSS PLACENTA AT VARIOUS GESTATION AGES*

FETAL AGE (WEEKS)	FETAL WEIGHT (GM.)	TOTAL Na OF FETUS (MG.)	DAILY WEIGHT INCREASE (PER CENT)	TOTAL Na RETAINED DAILY IN GROWTH OF FETUS (MG.)	Na SUPPLIED TO FETUS PER DAY (MG.)	SAFETY FACTOR
12	18.2	21	11.5	2.4	390	160
20	259	620	2.9	18	5600	310
30	960	2250	1.5	34	20600	610
40	2915	5100	1.1	56	63000	1130

*The daily per cent weight increase has been calculated from the data of Streeter,[6] and the sodium content of the fetuses is that found by Iob and Swanson.[7]

Discussion

As stated in the introduction of this paper, we have been primarily concerned with the following problems: (1) measurement of the permeability of the normal human placenta to sodium from early in gestation to term; (2) comparison of the permeability of the human placenta with that of other placentas of the hemochorial group; (3) measurement of the effects of disease on placental permeability and (4) evaluation of the supply of sodium to the fetus as this is related to the requirement for sodium during fetal growth.

The human placenta, as is true for all the placental types which have been studied with the tracer technique,[8] undergoes a very considerable increase in permeability to sodium as gestation proceeds. The peak in transfer rate per unit weight of placenta occurs at about the thirty-sixth week when it is approximately 70 times as great as at the ninth week, the earliest case in our series. This peak is followed by a rapid decline in permeability to term. These changes can be correlated with morphological changes which occur in the placenta during the process of aging. The illustrations of Fig. 2 are typical of placentas of twelve, nineteen, twenty-eight and forty weeks of pregnancy. They are all made at the same magnification (×155) and show clearly some of the important alterations in this organ as gestation progresses. At twelve weeks, the villi are large, relatively few in number and covered with a double layer of cells, the outer, syncytial and the inner, cellular. At nineteen weeks there is an increase in the number of villa, a decrease in their size and Langhans' layer has almost completely disappeared. The increase in total cross sectional area of the villi, together with thinning of their walls, continues through the twenty-eighth week to term. Higher magnification reveals in addition, as pregnancy proceeds, an increase in number of fetal capillaries within the stroma of the villus together with a decrease in the thickness of the capillary walls. The terminal sharp decrease in placental permeability is undoubtedly due in considerable measure to the deposition of fibrinoid over the surface of the villus. All of these morphological changes provide an interpretation of the observed changes in transfer rate per unit weight placenta.

The placenta of man in Grosser's classification[2] belongs to the hemochorial group as do the placentas of rabbit, rat and guinea pig. According to the results of Mossman,[9] the rabbit's placenta in the latter stages of pregnancy becomes

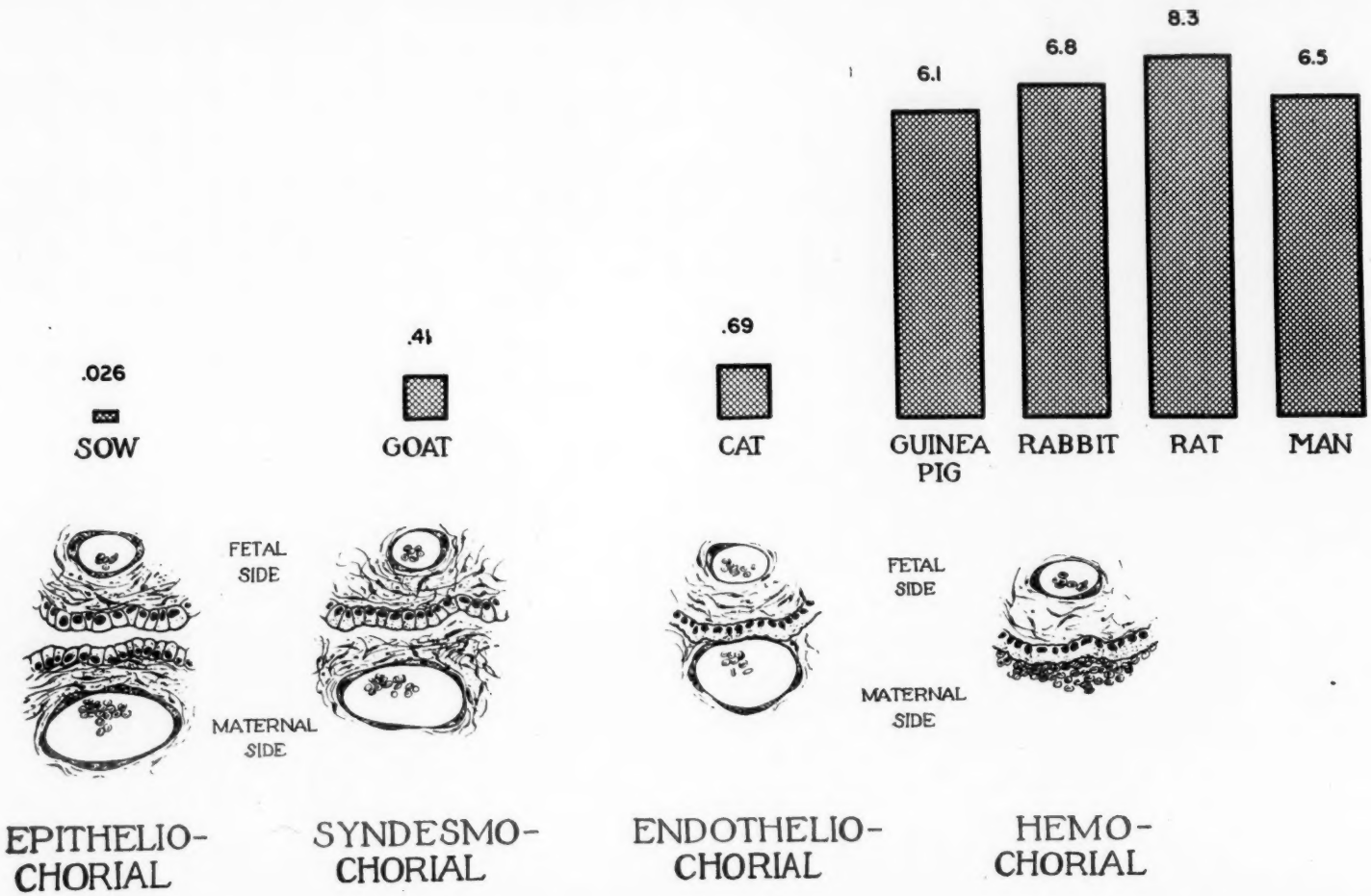


Fig. 3.—Variation of transfer rate of sodium per unit weight of placenta with the morphologic type of placenta. Numerical values give the milligrams of sodium transferred across a gram of placenta per hour as observed in each instance at the middle of the ninth-tenth of pregnancy. The relative magnitudes of the transfer rates are indicated by the relative areas of the dotted rectangles. The diagrams indicate the number and kind of tissue layers interposed between maternal and fetal circulation in each of Grosser's four groups.

Am. J. Obst. & Gynec. March, 1948

hemoendothelial and Mossman suggests that the same change may occur in the placentas of other rodents. Hard,[10] however, has obtained evidence using the phosphatase reaction that the placenta of the guinea pig remains hemochorial throughout gestation. The results on transfer of sodium across the human placenta afford a functional test of its morphological similarity to other members of the hemochorial group. Fig. 3 presents schematically the tissue layers interposed between maternal and fetal circulations in Grosser's four groups. Above the diagrams of the placentas there is indicated graphically the amount of sodium transferred per Gm. placenta per hour at the middle of the ninth-tenth of gestation. It is evident that the four placental types can be readily distinguished from one another by the differences in their permeabilities. It is also evident that the permeability of the placenta of man to sodium agrees closely with other members of the hemochorial group. Once again in our studies on placental permeability, Grosser's classification has proved its extraordinary usefulness in the interpretation and integration of our results.

Our experience with the effect of disease, anesthesia and labor on the permeability to sodium is rather meager and suggests only tentative conclusions. The permeability of the placentas from five patients with hypertension and two with cardiac disease was found to be normal. The transfer rate was independent of the type of anesthesia. Two cases in which transfer rates were measured during labor, just prior to the time of delivery, showed normal rates indicating that placental function is not remarkably disturbed during this period. A reduction of transfer rate was noted in one of two cases of pre-eclampsia and the rate was low in the single case of twins which was studied. In our opinion, more experience with sodium and other tracer materials is needed in these several conditions before reliable conclusions about placental function can be drawn.

The use of tracer substances permits the study of that aspect of fetal nutrition which is concerned with the quality of substances supplied to the fetus as this is related to the growth requirements of the fetus. The lowest safety factor (ratio of the amount of a substance supplied to a unit weight of fetus to the amount of that substance retained by the unit weight of fetus in its growth) for sodium has been observed in the sow and has a value of 3.5.[11] The highest safety factor for sodium observed prior to the studies reported here is in the guinea pig and has an average value of 50.[4] Man, in our experience, is unique in the extraordinarily high value of the safety factor which varies from 160 at twelve weeks to over 1100 at term; less than 0.1 per cent of the sodium which reaches the human fetus at term is retained, 99.9 per cent being returned to the maternal circulation. Man is unique also in that sodium is supplied at a constant rate, about 0.9 mg. per Gm. fetus per hour, from the twelfth week of pregnancy when the fetus is reproducing its weight at the rate of about 12 per cent per day to term when the daily per cent weight increase is only about 1 per cent. This is the single exception which has been found to the hypothesis that the fundamental principle underlying placental function is that the rate at which substances are transferred to a unit weight of fetus shall parallel the relative growth rate of the fetus.[9]

rectangles. The diagrams indicate the number and kind of tissue layers interposed between maternal and fetal circulation in each of Grosser's four groups.

Summary

1. Changes in rate of placental transfer per unit weight of placenta have been measured in normal pregnancies, using radioactive sodium, from the ninth week of gestation until term. The permeability of the placenta increases about 70 times during this period. The type of anesthesia was without effect on the rate which was also unaffected during labor immediately preceding birth. The permeability to sodium of the human placenta is like that of other members of the hemochorial group.

2. In a small series of cases, chronic hypertension and cardiac disease were without effect on the rate of transfer. One of two cases of pre-eclampsia showed a marked reduction of permeability.

3. The fetus receives across the placenta at the twelfth week of pregnancy 160 times, and at the fortieth week, 1100 times as much sodium as is incorporated in the growing tissues.

We are grateful to Dr. N. J. Eastman for his interest and generous cooperation.

References

1. Gellhorn, A., Flexner, L. B., and Hellman, L. M.: Am. J. Obst. & Gynec. **46**: 668, 1943.
2. Grosser, O.: Fruhentwicklung eihautbildung und Placentation, Munich, 1927, J. F. Bergmann.
3. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, 1931, Williams & Wilkins.
4. Flexner, L. B., and Pohl, H. L.: Am. J. Physiol. **132**: 594, 1941.
5. Flexner, L. B., Wilde, W. S., Proctor, N. K., Cowie, D. B., Vosburgh, G. J., and Hellman, L. M.: J. Pediat. **30**: 413, 1947.
6. Streeter, G. L.: Contrib. Embryol., Carnegie Inst. Washington **11**: 146, 1920.
7. Iob, V., and Swanson, W. W.: Am. J. Dis. Child. **47**: 302, 1934.
8. Flexner, L. B., and Gellhorn, A.: Am. J. Obst. & Gynec. **43**: 965, 1942.
9. Mossman, H. W.: Am. J. Anat. **37**: 433, 1926.
10. Hard, W. L.: Am. J. Anat. **78**: 47, 1946.
11. Gellhorn, A., Flexner, L. B., and Pohl, H. L.: J. Cell. & Comp. Physiol. **18**: 393, 1941.

THE BABY AS A PROBLEM IN PREMATURE DELIVERY*

N. W. Philpott, M.D., and F. J. Tweedie, M.D., Montreal, Que.
(From McGill University and Royal Victoria Hospital)

MUCH emphasis has been placed upon the importance of recognizing dystocia caused by malformation of the pelvic bones. This usually is referable to those cases near term who have a large-sized fetus and where there is a bony disproportion. But when we review figures of fetal deaths, we are impressed by the fact that a great proportion of these deaths occur in small babies where there is no bony disproportion. Soft tissue dystocia plays the important role.

Normal individuals possess a cervical canal which is the valve of the uterus. The cervical function in pregnancy is to hold the products of conception in their normal position. As maturity is approached the valve should release and allow the contents of the uterus to be expelled without causing undue obstruction. This is a gradual process which occurs in those weeks immediately preceding full term. Thinning of this lower uterine segment should normally be a non-painful procedure occurring before the onset of labor.

When labor occurs prematurely there is a great difference. The thick lower segment must be dilated by painful contractions. This is a tedious process and causes greater hazards to an immature fetus. Premature labor is frequently an accidental occurrence; it is unavoidable following some acute crisis or infection. These cases should be handled with extreme care.

The fetal mortality in vertex presentations where the baby is premature ranges far higher than those of mature infants. Complications are varied but the maximum danger occurs in the second stage of labor, relative to pressure of the soft malleable head against the resisting tissues of the pelvic floor. Mortality is still a great deal higher when the fetus presents as a breech, due to the fact that the diameters of the premature baby's hips or shoulders are less than those of the aftercoming head. Consequently, the head becomes compressed by a partially dilated cervix and by a lower tract which has not been adequately distended. A review of 500 breech cases in our Clinic showed interesting results.

Many obstetricians condemn bag induction. I agree that the indications are few. However, if labor occurs with the breech presenting, and the baby is premature of twenty-eight to thirty-four weeks' maturity, a bag induction should be considered as a proper dilator. In seven cases of this type, five live babies were obtained.

*Presented, by invitation, at a meeting of the Philadelphia Obstetrical Society, Feb. 6, 1947.

TABLE I. BREECH DELIVERY (500 CASES)

Total fetal mortality Cesarean or external version		13 per cent 26 cases	
		FETAL MORTALIY	
	CASES	NO.	PER CENT
Full term	403	31	7.6%
8 months	44	11	25%
7 months	27	22	81%

Certain conditions in the last trimester demand interruption of the pregnancy. Most obstetric techniques have been simplified during the last few years. But induction of labor has not been appreciably facilitated by improved methods. The obstetrician is frequently faced with the necessity of performing a premature delivery with no "near-perfect" method at his disposal.

TABLE II. INDUCTION OF LABOR BEFORE TERM IN ROYAL VICTORIA HOSPITAL

	1941-43 FETAL MORTALITY		1944-46 FETAL MORTALITY	
	NO.	PER CENT	NO.	PER CENT
Rupture of membranes	557	6.5%	528	6.2%
Medical	340	4.5%	374	4.7%
Medical & pituitrin	136	5.3%	116	7.0%
Bag induction	34	59.0%	19	57.0%

We are agreed that prophylaxis is the best form of treatment; possible prevention of those conditions which are prone to force induction should be further investigated. A nearer approach to maturity creates a better chance of survival unless some complicating factor outweighs this advantage.

Cesarean section is a quick and sure way of delivery. However, there are several pitfalls, especially in a French-Canadian environment. This operative procedure causes definite limitation to the size of the patient's family. But more important are the dangers of hemorrhage or sepsis which must always be considered. Sometimes this operation is the method of choice. It is the "trump card" only to be used at the proper time.

Delivery per vagina necessitates induction of labor. If the patient is approaching full term, most methods of induction are equally efficient. The difficulty encountered in the induction of labor is usually in direct proportion to the number of days the patient is lacking with reference to her appointed time of delivery. This is easily explained. Necessary stimulation to uterine contraction is lacking. In addition, the thinning of the lower uterine segment has not taken place. Induction of premature labor at any period in the last trimester should only be instigated on account of a definite medical indication. Too frequently labor is induced to please the patient, or even to accommodate the doctor who is in charge of the case.

With reference to cephalopelvic disproportion cases, we do not induce labor unless the degree of disproportion is only moderate and the patient is near full term. Before induction, we make certain of the disproportion by vaginal examination; in addition we ascertain the condition of the cervix

and make certain that it will not offer too much obstruction. Simple rupture of the membranes is the method of choice except when there is marked disproportion and delivery by cesarean section is indicated.

Toxemia is fairly frequent in our hospital. Most of these cases are referred from outlying districts where they have had inadequate or no prenatal instruction. Prevention of the disease is the best approach when it is possible. Frequent antenatal visits and proper supervision are most essential. We heartily agree with Dr. Winslow Tompkins, in regard to high protein intake with reference to the prophylaxis and treatment of toxemia. Supportive treatment varies little from other clinics.

Induction of labor is carried out only when indicated. It is usually by simple rupture of the membranes. If the patient is severely toxic and she is not near term, we sometimes use the intraovular insertion of a small rubber bag of approximately 150 c.c. content. We fully realize that this type of delivery creates a possible 50 per cent fetal mortality. Cesarean section is occasionally performed for combined indications, and in the nephritic type of toxemia where future pregnancies do not promise any better fetal results.

Placenta previa and fetal mortality go hand in hand. Maternal hemorrhage causes fetal anoxia; there is the additional factor that prematurity also plays a role in producing a delicate baby. Even suspect cases are examined in the operating room. This is to prevent additional or needless loss of blood. The marginal type is most commonly treated by simple rupture of the membranes. More pronounced types of placenta previa are delivered by cesarean section. Anoxia in the baby is a frequent sequela of maternal blood loss. This is best treated by transfusing the mother with whole blood before operative procedures are instigated. This should be repeated as frequently as indicated. Administration of oxygen to the mother during operation is very beneficial.

Space does not permit discussion of Rh iso-immunization. Induction of labor or, sometimes, cesarean section before the baby becomes overwhelmed with antibodies is the wise procedure. Antibody studies can now give a fairly definite prognosis in most cases. A marked rise or variation in the agglutinating or blocking antibodies is indication for interruption of pregnancy any time after the baby is viable.

In June, 1946, Rivett reported successful results in hydramnios cases by means of repeated aspiration of fluid from the amniotic cavity. This is done through the abdominal wall with little risk. We have completed three cases since that time. One baby is normal, another had marked "clubfeet" and absence of several fingers and toes, while the third was a marked microcephalic with patent ventricular septum. This procedure is only indicated when the fetus is considered normal but small. If the development is not sufficient to assure viability, sometimes aspiration of excess fluid will enable the baby to reach the viable period.

Diabetes complicating pregnancy is a cause for worry. Fetal mortality is very high even in the controlled patient. Rabinowitch points out several important facts:—

1. Those patients only on diet control experienced as high a fetal mortality as the more severe types taking insulin.

2. The high incidence of diabetes plus toxemia due to marked increase in prolan found by White and Hunt could not be substantiated. Only 12 per cent of our cases showed evidence of toxemia.

3. Normal deliveries were usually postmature and were accompanied by the highest fetal mortality. Labor induced before term gave better results. The lowest mortality (8.3 per cent) was in the group where a cesarean was done before term.

TABLE III. DIABETES MELLITUS (RABINOWITCH)

Relationship Between Mode of Delivery and Fetal and Neonatal Mortality. (64 deliveries in Montreal)

	PRIMIPARAS			MULTIPARAS		
		DEATHS			DEATHS	
MODE OF DELIVERY	NO.	NO.	PER CENT	NO.	NO.	PER CENT
Natural	3	2	66.6	13	4	30.7
Labor induced before term	11	2	18.1	4	1	25.0
Cesarean section	9	1	11.1	24	2	8.3
Total:	23	5	21.7	41	7	17.1

Many authors include syphilis as a common cause for prematurity. There have been 512 proved syphilitics in our obstetric service during the last thirteen years; this is an incidence of approximately 2 per cent. Practically every case has received adequate treatment during pregnancy. This is possibly why we do not see many premature babies due to syphilis. We had only three premature babies from syphilitic mothers in 1946. There were forty-one active syphilitics during the year. All cases had received antisyphilitic treatment.

The Baby

We have prepared certain charts which are self-explanatory. Table IV gives the general maternal and fetal mortality. During the six-year period from 1941 to 1946 there were 572 fetal deaths, and the clinical diagnosis is tabulated. Two hundred six of these deaths occurred in premature babies, an incidence of 36 per cent. The more accurate pathologic diagnosis is listed for 286 cases who had autopsy examinations. These excluded those cases where the infant was badly macerated and those where autopsy examination was refused by the parents. Of the 286 cases where autopsies were performed, 58 per cent occurred in premature babies:—

TABLE IV. 1941-1946

Total deliveries		15,691
Maternal mortality	1941 to 1943	.17%
	1944 to 1946	.11%
Fetal mortality	1941 to 1943	3.7%
	1944 to 1946	3.5%

Clement Smith and others have shown that the premature baby differs greatly from the full-term infant. There is excessive accumulation of organic acids in the blood. Renal immaturity decreases kidney function, and there is a limitation of water available for urinary secretion. Hepatic immaturity

causes decreased liver function. Blood studies show a comparative anemia with a predisposition to developing anoxia and hemorrhage in the brain and liver. The immature lung is frequently associated with patchy atelectasis which predisposes to subsequent respiratory infection. Altogether the premature baby is a liability.

Antenatal pediatrics is a new term, but the significance is old. We are all agreed that the general physical condition of the pregnant woman is often reflected in the condition of the offspring. This is especially true relative to the premature baby. Prophylaxis of preventable conditions frequently is assured by means of adequate antenatal care. Nutrition is important in all cases. Abnormal findings should be heeded and the complication should be promptly treated. Judicious use of sedatives during labor, type of delivery and well-chosen anesthetic all play an important role in the result obtained.

It has been shown that the incidence of premature infant mortality varies inversely to the size of the babies. We also emphasize the fact that deaths in premature infants become progressively less frequent with each hour of life. Over 50 per cent of all neonatal deaths in premature babies occur during that first twenty-four hours following delivery. Some of these deaths are preventable. This is relative to: conditions caused by anoxia, aspiration of mucus or other fluids, insufficient incubation, and too many contacts.

The obstetrician and pediatrician should work in harmony. Their combined invaluable experience is most essential to obtain good results. This necessitates more than an average knowledge relative to the care of the newborn baby; both obstetric and pediatric interns should receive adequate instruction in the care of the newborn baby. Beck has pointed out the advantages of a definite system. It has also been emphasized in the report of the Illinois State Plan where excellent results were obtained by developing an organization which is supervised jointly by the obstetrician and the pediatrician.

It should be emphasized, however, that the authority and interest of the obstetrician must be maintained in the care of the newborn infant. This is essential due to the fact that effects of pregnancy, labor, and delivery play the major role in the eventual outcome of the offspring. Most fetal deaths occur during that period when the obstetrician is in complete charge, regardless of what system is followed during the neonatal period.

Our hospital has a staff pediatrician who supervises the routine in all nurseries. A resident who is trained in the care of the newborn is in charge of all babies. He reports to the staff pediatrician as well as to the obstetrician who is in charge of the individual case. This resident is present at all difficult deliveries such as cesarean births, difficult forceps cases, and those complicated by placenta previa or toxemia. He supervises and treats all babies from birth until the time of discharge.

Treatment of the premature baby is most important. There are two phases: (1) First hour of life, and (2) Neonatal period in the nursery.

Very small babies are fed every two hours. Poor feeders have a three-hour schedule, and good feeders receive feedings every four hours.

Clysis of plasma or glucose and saline is given for dehydration or to stimulate weight gain. The hemoglobin is estimated at least every seven days. Iron therapy is given when indicated. Whole blood transfusions are used when conditions warrant; this is a fairly common procedure in the premature nursery, and the indications have become more numerous.

Our premature nursery has completed three years in operation. For this reason I have taken two three-year periods for comparison. These periods are 1941 to 1943 and 1944 to 1946, inclusive.

The most significant improvement is in the fewer number of deadborn infants in the period from 1944 to 1946. General fetal mortality as well as premature deaths have decreased slightly. It should be emphasized, however, that the incidence of complicated cases has increased considerably in the last three years in our clinic. This is due to the fact that outside doctors would rather not handle this type of case and they are referred to our hospital. For example our admissions of hemolytic disease of the newborn have increased over 200 per cent.

Many of the deaths could not be prevented, but a great number are included which should be considered as preventable. It is interesting to note that only three babies died from effects of syphilis. There were 206 active syphilytics delivered in this series. Only six did not receive antisyphilitic treatment.

TABLE V. PREMATURE BABIES WEIGHING 1,000 TO 2,500 GM.

Total number		912
Incidence		5.7%
Mortality	1941 to 1943	24.3%
	1944 to 1946	21.0%
Five (5) babies under 1,000 gm. survived.		

TABLE VI. SUMMARY OF INFANTS UNDER 1,000 GM. AT BIRTH

CASES	BIRTH DATE:	BIRTH WEIGHT (GRAMS)	DISCHARGE DATE:	DISCHARGE WEIGHT: (GRAMS)
1. Baby S.	Oct. 6/44	660	Feb. 13/45	2340
2. Baby Bl.	Dec. 10/44	940	Mar. 1/45	2400
3. Baby Bll.	Dec. 10/44	900	Mar. 1/45	2340
4. Baby D.	Aug. 2/45	930	Nov. 29/45	2340
5. Baby P.	Sept. 15/46	990	Dec. 21/46	2660

The premature babies were classified only as those between 1,000 to 2,500 Gm. This coincided very well with estimation from the twenty-eighth to the thirty-sixth week of pregnancy. However, there were seventeen babies admitted to the premature nursery, and they all weighed less than 1,000 Gm. Five of these infants are still alive; the smallest weighed 660 Gm. at birth and it is now over two years of age. This is particularly significant in view of the fact that Haas reports only fifty-seven cases in the literature which survived and also weighed less than 1,000 Gm. at birth.

Our premature mortality rate is slightly higher than figures given by the Long Island College Hospital and the Hahnemann Hospital of Philadelphia. But we have had better success with the very small babies. We cannot boast of a great reduction in mortality during the last three-year period seeing that it dropped only 3 per cent. However, the reduction is important due to the fact that incidence of complicated cases in our clinic has increased considerably during this three-year period. In addition, it should be mentioned that several babies were considered as nonviable in the 1941-43 period. There were 20 babies which were approximately 1,000 grams but they were not weighed. These died shortly after birth, and several of them were indexed as nonviable. In the period from 1944-46 all babies were weighed and the uncorrected mortality includes every baby weighing between 1,000 and 2,500 grams.

Summary

1. Induction of premature delivery should be carried out only on acount of a definite indication.

2. Adequate equipment and trained personnel are essential for a premature nursery.

3. Breast milk bank and blood bank facilities are useful adjuncts.

4. Fetal mortality can best be improved by the combined efforts of the obstetrician and pediatrician.

We are grateful for the cooperation and suggestions of Dr. Graham Ross, Pediatrician-in-charge.

References

Beck, Alfred C.: Am. J. Obst. & Gynec. **51**: 173-183, 1946.
Dana, Ethel S.: Am. J. Obst. & Gynec. **51**: 329-342, 1946.
Smith, Clement H.: Physiology of the Newborn, 1945, Charles C Thomas.
Haas, R. L.: Am. J. Obst. & Gynec. **50**: 406-411, 1945.
Parsons, L. J.: J. Obst. & Gynaec. Brit. Emp. **53**: 1-16, 1946.
The Illinois Plan for Premature Infants, Illinois M. J. **88**: 117-118, 1945.
Bloxsom, Alan: J. Pediat. **28**: 418-421, 1946.
Redman and Gates: Hahnemann Monthly **81**: 135-141, 1946.
Rivett, L. C.: Am. J. Obst. & Gynec. **52**: 890-894, 1946.

Discussion

DR. CARL BACHMAN.—I wish to emphasize the notion that the premature infant is handicapped not only by its prematurity, but also by the fact that, in the great majority of instances, it is also an ill or damaged infant. Of the factors which militate against its survival, its prematurity per se is perhaps the least important.

The pathologic factors are twofold. The first is the disease or abnormality of the mother, or of the ovum itself, which is responsible for interrupting the infant's intrauterine development prematurely. Who can say that the fetus of a toxic mother, or of one who suffers an antepartum placental hemorrhage, is not likely to be handicapped by these factors? Yet if one reviews one's experience with premature delivery, one must be struck by the fact that the overwhelming majority of them occur, whether spontaneously or by design, because of abnormalities of this character accompanying the gestation.

The second factor is the frequently tedious, and therefore often traumatic character of premature labor and delivery. Some of the factors which make it so have been mentioned by Dr. Philpott. Because of them, our Staff at the University of Pennsylvania have become increasingly loath to resort to induction of premature labor when there is a legitimate in-

dication for interrupting pregnancy, but prefer to do an abdominal delivery. We prefer it because we have found that more infants survive such a method of delivery, yet the maternal risk has not been increased. We shall continue to do this, under these circumstances, until and unless methods can be developed for inducing and obtaining premature labors that are superior to current ones.

DR. PHILPOTT (closing).—I think Dr. Bachman and I are in agreement with regard to induction of labor and the results thereof. I would only like to define our attitude in Montreal regarding inducing labor. We are in a predominantly French Canadian community and that must be borne in mind. My reaction to cesarean section is that a good many can do one or two cesareans, but not eight or nine in the same patient. Our community is very orthodox in religion. They do not believe in ligation of the tubes and we do not do more cesareans on that account. One or two cesareans can be done safely, but beyond that it is dangerous. Over 50 per cent in the community are Roman Catholics. Most will not consent to ligation of the tubes, and it is necessary to follow the course I have presented, and we have resorted to that. The fewer labors we induce the better results we will get. The premature baby is another problem. It is often a sick baby, it has gone through a tedious labor, and as a result of premature delivery is not fully developed, the renal system and the various other systems are immature, and all in all it is an entirely different problem from the full-term baby. With reference to Dr. Montgomery's question, we have been very pains taking and definite about prematurity.

THE FATE OF THE LIVING VIABLE BABIES IN EXTRAUTERINE PREGNANCIES

MAX SUTER, M.D., JACKSONVILLE, FLA., AND CELESTE WICHSER, M.D., NEW ORLEANS, LA.

(From the Departments of Obstetrics and Gynecology, Louisiana State University School of Medicine and Charity Hospital of Louisiana)

THIS paper was written with the idea of determining, as nearly as possible, from the limited clinical material available at Charity Hospital of Louisiana, at New Orleans, and from a survey of the literature the fate of the viable babies delivered from extrauterine pregnancies. Only cases of twenty-eight or more weeks' gestation with babies born living were selected. Forty-one additional cases of living, viable babies in abdominal pregnancies are presented graphically from the literature to supplement those recorded by Sittner,[6] Hellman and Simon,[2] and Mitra.[4] Four new cases are presented from Charity Hospital, at New Orleans, in addition to those recently reported by Beacham and Beacham.[1]

Winckel[7] in discussing the deformities of extrauterine pregnancies stated that 75 per cent of all the deformed children included deformities of the head, half of them deformities of the lower extremity, and 40 per cent deformities of the upper extremity. The more sheltered thorax, abdomen, and genitourinary system were deformed in only 3 or 4 per cent of the babies. Of 316 living, viable babies reviewed by Hellman and Simon[2] in 1935 from the world literature, including those previously reported by Sittner, a specific statement as to the development of the babies was made in only sixty-four cases. Of these, thirty, or 46.6 per cent, were found to be deformed. One hundred fifty, or 44.3 per cent, of the babies survived for eight days or more, and of these a specific statement as to the development was made in forty-one babies; fifteen, or 36.6 per cent, were found to be deformed. Stabler,[5] in 1938, reviewed 266 cases from the world literature. Of 266 living, viable babies delivered from abdominal pregnancies, 152, or 57.1 per cent, lived for eight days or more. The fate of only one was undetermined. Twenty-eight, or 10.5 per cent, of these babies were recorded as being deformed. Lelling,[3] in reviewing 106 cases in 1938, found that development was mentioned in only 82 of the 106 babies. Of these, thirty-two, or 39 per cent, were recorded as deformed. Mitra,[4] in reviewing the world literature on advanced extrauterine pregnancies in 1942, found that of 179 extra-uterine pregnancies of more than five months' gestation only 23.5 per cent delivered living, viable babies. Of these, a specific statement as to the development was made in thirteen, ten of which were recorded as being deformed. Beacham and Beacham,[1] in a report of twenty abdominal pregnancies from Charity Hospital, at New Orleans, found that only three, or 15 per cent, delivered living, viable babies.

In our review of forty-one additional cases in the literature we found that a specific statement as to the development was made in thirty-one babies. Twelve, or 38.7 per cent, of these babies were found to be deformed. Ten, or 24.3 per cent, of the babies died before the eighth day.

Four new cases of extrauterine pregnancies with living, viable babies are reported from Charity Hospital.

Case Reports

CASE 1.—E. P. The patient, a Negro female, gravida i, para 0, whose last menstrual period was Nov. 23, 1944, was admitted to Charity Hospital on July 25, 1945, with the chief complaint of pain in the lower abdomen, and vomiting. When she was three to four months pregnant, the patient had an attack of severe lower abdominal pain associated with fainting from which she recovered spontaneously.

The patient's blood pressure was 135/100. Her abdomen was the size of an eight months' pregnancy, and fetal parts were quite superficial. The abdomen was markedly tender. Fetal heart tones were 140 in the left lower quadrant. Sterile vaginal examination was done. The cervix was pushed forward, soft, long, and patulous. Membranes or fetal parts were not felt through the cervical os. A shoulder was felt posterior to the cervix. Urinalysis was negative. Hemoglobin was 10 grams. X-ray revealed cephalic presentation with back to right. No uterine shadow was seen.

Preoperative diagnosis: abdominal pregnancy.

Laparotomy was performed on July 25, 1945. Uterus was found to be the size of a ten weeks' pregnancy, with a 5 cm. fibroid extending to the left. A male infant was free in the abdominal cavity without a sac. A small amount of fluid was found in the abdominal cavity. Male baby weighed 4¾ pounds, and had a deformed head and clubfeet. He was in poor condition after birth and died the same day. The cord was tied off close to the placenta and the abdomen was closed without drainage, leaving the placenta in situ.

Postoperative course was afebrile after the first day, and the patient was discharged on the seventeenth day, at which time the placental mass had not regressed in size.

Patient was readmitted on Feb. 7, 1946, with the chief complaint of pain in the abdomen. She was afebrile during the stay in the hospital and was operated on Feb. 19, 1946, for removal of retained placenta. The placenta was found to be attached to the cul-de-sac, posterior surface of the right broad ligament, lateral wall of the pelvis, posterior pelvic wall, rectosigmoid, and mesoappendix. In order to remove the placenta it was necessary to do a subtotal hysterectomy, bilateral salpingo-oöphorectomy, and appendectomy. The patient was discharged on Feb. 28, 1946, in good condition.

CASE 2.—V. R. The patient, a 28-year-old Negro female, whose last menstrual period was April 1, 1946, was admitted to Charity Hospital on Jan. 8, 1947, with a history of recurrent abdominal pains every two to three minutes, nausea, and vomiting. On September 17 the patient had an episode of bleeding. Since September, 1946, she had been having periodic attacks of pain in the lower abdomen more severe on the right side, which were relieved by vomiting and aggravated by any activity. The patient said that she felt the baby move only on the right side.

Blood pressure was 110/80. Heart and lungs were negative. Abdomen was enlarged to the size of a term pregnancy, vertex presentation, head floating. Fetal heart tones were best heard in the right lower quadrant, and their rate was 152. The patient was recorded as having hard pains every three minutes. Urinalysis was essentially negative. Hemoglobin was 9.5 grams.

Diagnosis of breech presentation was made which was confirmed by x-ray. X-ray also showed a peculiar shaped occiput in left flank.

On Jan. 9, 1947, the cervix was found to be soft, long, and would barely admit one finger. Exploration of uterine cavity revealed no membranes nor fetal parts. It was found to be about 10 cm. long.

Patient had a laparotomy on Jan. 9, 1947, with preoperative diagnosis of abdominal pregnancy. When the abdomen was opened, the fetal sac was found in the abdominal cavity. This was opened and a living, male infant weighing 6 pounds was delivered by breech extraction. The baby had a plastic deformity of the head and a right clubfoot, and contraction deformities of both arms. The placenta was attached to the bowel, the omentum, and the left cornual portion of the uterus. The placenta was removed with minimum amount of bleeding. The abdomen was closed without drainage.

Postoperative course was essentially afebrile. Five-month check-up revealed that both mother and baby were getting along well.

CASE 3.—E. McC. The patient, a 23-year-old Negro female, gravida i, para 0, whose whose last menstrual period was June 7, 1946, was admitted to Charity Hospital on March 23, 1947, with the chief complaint of pain in the abdomen for the past two days.

The heart and the lungs were negative. The abdomen was that of a breech at term. Fetal heart tones were 140 and best heard in left upper quadrant. There was marked costovertebral tenderness. During her stay in the hospital, the patient developed enlargement of the abdomen with marked dyspnea.

Vaginal examination disclosed the cervix undilated and uneffaced. No membranes nor fetal parts were felt through the pelvis.

Temperature was 101° F., pulse 130; blood pressure 130/72. Urine was essentially negative. Hemoglobin was 11.8 grams. X-ray revealed one fetus outside of pelvis, breech presentation. No uterine wall could be made out.

Preoperative diagnosis: Abdominal pregnancy at term.

Patient had a laparotomy performed on March 25, 1947, at which time the placenta was found attached to the left cornual portion of the uterus. Some uterine muscle fibers extended up alongside of the fetal sac, but did not entirely cover it. When the sac was opened, it was found to be made up of three definite layers; the outside one was rather fibrous in character. The sac was opened and an 8 pound 15 ounce apparently normal living male child was delivered, who died in a few minutes. In order to remove the placenta, a left salpingo-öphorectomy and supracervical hysterectomy were necessary. The mother was discharged in good condition on the tenth postoperative day.

CASE 4.—D. T. The patient, a 29-year-old Negro female, gravida v, para iii, had not menstruated since her last pregnancy in 1946. She was admitted to Charity Hospital on May 9, 1947, with a history of having had convulsions that morning and having had some sedation given her by her private physician. On admission she was semistuporous and complained of pain in the lower abdomen. She had a productive cough and expectorated blood-tinged sputum. She had been dyspneic for some time.

Temperature was 99.4° F.; pulse 160; blood pressure 164/128. There was marked edema of legs and moderate edema of anterior abdominal wall. The lungs had a few râles at both bases. The heart was enlarged 3 cm. to the left midclavicular line. The abdomen was the size and contour of a term pregnancy. No definite fetal heart tones were heard.

At vaginal examination the cervix could not be felt because it was high and anterior. There was a firm mass about 10 cm. in diameter filling the cul-de-sac.

The urine showed three plus albumin; hemoglobin 11.5 Gm.; venous pressure 115 millimeters of water. X-ray revealed a fetus lying between transverse and in a breech. An electrocardiogram was strongly suggestive of myocardial disease. Kline test was positive.

TABLE I. SUMMARY OF CASES SINCE 1930

DATE OF OPERATION	OPERATOR	PLACE OF OPERATION	RESULT TO MOTHER	STATUS OF FETUS	SPECIAL NOTES; BIBLIOGRAPHY
Feb. 2, 1930	Reeb	Strassburg, Germany	Recovered	32 weeks; lived; normal	Kries, J. Reb.: Franç. de Gynec. et Obst. **32**: 89, 1937.
Dec. 29, 1930	LaRoque	Richmond, Va.	Recovered	40 weeks; lived; normal	Ware, H. H.: New York State J. Med. **36**: 1943, 1936.
Mar. 1, 1931	Gushue and Taylor	Taihoku, Formosa	Died (from ileus and shock)	44 weeks; female, well formed, normal, 7 lbs.	Gushue-Taylor: Brit. M. J. **1**: 640, 1942.
Apr. 16, 1932	McNeile	Los Angeles, Calif.	Recovered	28 weeks; living; no deformities	McNeile, L. G.: West. J. Surg. **45**: 119, 1937.
Dec. 11, 1932	Beal and Cassell	Gemdar, South India	Recovered	40 weeks; gasped and died; deformity of left foot; 7 lbs.	Beal, A. M., and Cassell, N. S.: J. Iowa M. Soc. **30**: 445, 1940.
Sept. 6, 1933	Ziegler	Pittsburgh, Pa.	Recovered	40 weeks; living male, normal, 7 lbs. 2 oz.	Eisaman, J. R., and Ziegler, C. E.: J. A. M. A. **104**: 2175, 1935.
July 20, 1934	Eula and Eno	Shanghai	Died	40 weeks; asymmetry of head; deformity of right knee; female, 7 lbs. 6½ oz.	Eno, E., and Towers, A. E.: Chinese M. J. **51**: 33, 1937.
Jan. 9, 1935	Woods	Augusta, Ga.	Died (14 hr.)	38 weeks; living; normal, 5 lbs. 2 oz.	Woods, E. B.: AM. J. OBST. & GYNEC. **32**: 155, 1936. (Autopsy done.)
Feb., 1935	Bondurant	Cairo, Ill.	Recovered	40 weeks; living, normal, 4¾ lbs.	Bondurant, F.: Illinois M. J. **71**: 480, 1937. (Combined full term; extra and intrauterine gestation. Intrauterine child had congenital syphilis; weight 3½ lbs.; lived 5 days.)
April 15, 1935	McNeile	Los Angeles, Calif.	Recovered	24 weeks; lived 24 hours; normal	McNeile, L. G.: West J. Surg. **45**: 119, 1937.
June 11, 1935	Wilson	Dubban, India	Recovered	32 weeks; lived; normal, 5¼ lbs.	Wilson, A. S.: Proc. Roy. Soc. Med. **29**: 1651, 1936.
Sept. 11, 1935	Anderson	Lucknow, India	Recovered	4 weeks; lived 15 min.; 6 lbs.	Anderson, M.: Brit. M. J. **2**: 589, 1936.
Sept. 11, 1935	Colistro	Pasteur Hospital Uruguay	Died	40 weeks; baby alive at operation	Colistro: Arch. Urug. de Med. cir y Espacialid **14**: 141, 1939. (Did not say if baby continued to live.)
Dec. 3, 1935	MacGregor	Brooklyn, N. Y.	Recovered	38 weeks; living; not normal, 2,660 Gm.	MacGregor, A. S.: AM. J. OBST. & GYNEC. **34**: 1030, 1937.

Feb. 1, 1936	Lailey	Toronto, Canada	Recovered	44 weeks; lived; had one club-foot; no other deformity; 11 lbs. 1 oz.	Lailey, W. W.: Canad. M. A. J. **36**: 67, 1937.
Mar. 12, 1936	Lelling and Lendemann	Barbara-krankenhouse, Germany	Died	7 mo.; not resuscitated; club-foot	Lelling, E.: Zentralbl. f. Gynäk. **62**: 2209, 1938.
Mar. 23, 1936	Shen Shi Ying	Shanghai	Recovered	48 weeks; died in 6 hr.; head asymmetrical; cleft palate	Eno, E., and Towers, A. E.: Chinese M. J. **51**: 33, 1937.
June 7, 1936	Hoffman	Charleston, West Va.	Recovered	40 weeks; lived ½ hr.; baby cyanotic; 4 lbs. 10¾ oz.	Hoffman, W. E.: West Virginia M. J. **33**: 496, 1937. (Child has a marked distortion of head; nose is flattened against face, and right nares is closed; flexion deformity of right elbow; right foot is everted.)
June 25, 1936	Salamanca	Mexico City	Recovered	39 weeks; lived 17 hr.; 6 lbs. 2 oz.	Salamanca, A. G.: J. Internat. Coll. Surgeons **3**: 271, 1940.
May 1, 1937	Bruck	Grunberg	Recovered	Living; normal; 3,300 Gm.	Stavenhagen, Med. Klin. **33**: 1609, 1937.
June 10, 1938	Harkness	Mevanza, Tanganyika Territory	Died	40 weeks; not resuscitated; normal, 7½ lbs.	Harkness, J., and Fairfax, B.: Brit. M. J. **2**: 1044, 1938. (There was question if baby was living. Mother died at surgery. Head slumped into vagina.
Aug. 27, 1938	Hamblen	Spokane, Wash.	Recovered	40 weeks; lived 3 hr.; normal, 5 lbs. 2 oz.	Hamblen, R. N.: West. J. Surg. **48**: 310, 1940.
Sept. 12, 1938	Hains	Bundaberg, Queensland	Recovered	Right hip was turned in; 3,200 Gm.	Hains, I. C.: M. J. Australia **1**: 268, 1939.
March, 1939	Cunningham	Ireland	Recovered	36 weeks; lived; 4 lbs. 4 oz.	Cunningham, J. F.: Irish J. M. Soc., 846, 1939.
Mar. 18, 1939	White and Clark	Asheville, N. C.	Recovered	40 weeks; lived; normal	White, R. A.: North Carolina M. J. **2**: 87, 1941.
Mar. 28, 1939	Nicodemus	Danville, Pa.	Recovered	38 weeks; viable; lived; female 4 lbs. 9 oz.	Nicodemus, R. E., and Carrigg, L. G.: Am. J. Obst. & Gynec. **39**: 153, 1940.
July 18, 1939	Mayer and Marino	New Orleans, La.	Recovered	42 weeks; lived; normal, 7 lbs. 13 oz.	Beacham, W. D., and Beacham, D. W., Obst. & Gynec. Survey **1**: 777, 1946.
Aug. 4, 1939	Sprague and Chappel	Athens, Ohio	Recovered	36 weeks; lived 48 hr.; female, 7 lbs. 2 oz.	Sprague, J. R., and Chappel, M. R.: Ohio State M. J. **36**: 520, 1940. (Child had asymmetrical head and equinus varus.)
Nov. 16, 1939	Renner	Goodland, Kan.	Recovered	40 weeks; normal, 6 lbs. ¾ oz.	Renner, M. J.: J. Kansas M. Soc. **42**: 245, 1941.

TABLE I—CONT'D

DATE OF OPERATION	OPERATOR	PLACE OF OPERATION	RESULT TO MOTHER	STATUS OF FETUS	SPECIAL NOTES; BIBLIOGRAPHY
Oct. 4, 1939	Nicholls	Norfolk, Va.	Recovered	40 weeks; male, normal, 10 lbs. 3 oz.	Nicholls, R. B.: AM. J. OBST. & GYNEC. **42**: 341, 1941.
Feb. 25, 1941	Lin	Foochow, Fukien	Recovered	40 weeks; lived 2 hr.; asymmetrical face, right elbow; knee could not be straightened	Lin, A. Y.: Chinese M. J. **62**: 383, 1945.
July 26, 1941	Slatover	Manchester, England	Recovered	40 weeks; lived; normal female, 8 lbs. 10 oz.	Slatover, M. L.: Brit. M. J. **1**: 669, 1942.
Sept. 30, 1941	Guerriero and Hughes	New Orleans, La.	Recovered	32 weeks; living	Beacham, W. D., and Beacham, D. W.: Obst. & Gynec. Survey **1**: 777, 1946. (L-41-42400, Case XII.)
Oct. 1, 1941	Strumpf	Jacksonville, Fla.	Recovered	29 weeks; living; full term?	Strumpf, I. J.: AM. J. OBST. & GYNEC. **45**: 350, 1943.
Dec. 31, 1941	Lucas	Walsall, England	Recovered	34 weeks; lived; normal male, 5 lbs. 10 oz.	Lucas, C. F.: Brit. M. J. **1**: 722, 1942.
Mar. 6, 1943	Rabago	General Hospital, Mexico City	Recovered	28 weeks; twins, one in uterus; one in cul-de-sac; female in cul-de-sac lived	Rabago: Cir. y. Cirujanos **12**: 27, 1944.
Dec. 18, 1943	Rose	Miami, Fla.	Recovered	34 weeks; lived; normal; 5 lbs. 2½ oz.	Rose, M. J.: J. Florida M. A. **31**: 475, 1945.
Mar. 7, 1944	Greene	Memphis, Tenn.	Recovered	40 weeks; lived only short period	Greene, G. G.: South. M. J. **38**: 747, 1945. (Case No. 3.)
Feb. 19, 1945	Morgan and Keevil	Newport, Montreal	Recovered	36 weeks; lived 1 hr.; male	Morgan, R. G., and Keevil, N. L.: Brit. M. J. **2**: 649, 1945.
June 7, 1945	Goodin	Fort William Ontario	Recovered	40 weeks; male, 7 lbs.; lived 21 hr.; died of atelectasis	Goodin, P.: Canad. M. A. J. **54**: 483, 1946. (Baby was a livid-grey color and could not be made to cry.)
July 8, ?	Novey	Baltimore, Maryland	Died	40 weeks; living; marked bilateral deformities of feet; weight 5 lbs. 8 oz.	Novey, M. A.: Surg., Gynec. & Obst. **66**: 671, 1938. (Case 4, A. B., Negro, aged 31 years.)

A laparotomy was performed on May 13, 1947, with preoperative diagnosis of abdominal pregnancy versus uterine fibromyomas with intrauterine pregnancy. The fetal membranes were found free in the abdominal cavity. The membranes were opened and a grossly deformed living baby was found which died in thirty minutes. The placenta was attached to the uterus posteriorly between the broad ligaments, to the right iliac fossa, posterior abdominal structures, and small bowel. The cord was cut short. The placenta was left intact and the abdomen was closed without drainage.

On her sixteenth postoperative day the patient is in good condition but is still febrile.

Conclusions

Only about one-fourth of all the extrauterine pregnancies diagnosed after the fifth month of gestation will result in viable, living babies. About one-third of all these living, viable babies delivered from extrauterine pregnancies will have major or minor deformities including those which were incompatible with life. Approximately half of all the viable, living babies delivered from extrauterine pregnancies will survive eight days or more.

Summary

All the available literature on extrauterine pregnancies resulting in viable, living babies is reviewed to determine their ultimate fate.

Forty-one cases are tabulated from the literature to supplement those previously summarized.

Four new cases of extrauterine pregnancies with living, viable babies are reported from Charity Hospital of Louisiana, at New Orleans.

The authors wish to acknowledge their appreciation to Drs. Adolph Jacobs, D. W. Goldman, and E. L. King for use of cases on their services.

References

1. Beacham, W. D., and Beacham, D. W.: Obst. & Gynec. Survey **1**: 777, 1946.
2. Hellman, A. M., and Simon, H. S.: Am. J. Surg. **29**: 403, 1935.
3. Lelling, E.: Zentralbl. f. Gynäk. **62**: 2209, 1938.
4. Mitra, S.: Calcutta M. J. **39**: 1 and 43, 1942.
5. Stabler, F.: Brit. M. J. **1**: 779, 1938.
6. Sittner: Quoted from Hellman and Simon.[2]
7. Winckel, V.: Quoted from Lelling.[3]

ANTEPARTUM HEMORRHAGE*

ROBERT A. KIMBROUGH, M.D., PHILADELPHIA, PA., AND BROCK D. JONES, M.D., NORFOLK, VA.

(From the Division of Obstetrics and Gynecology, Pennsylvania Hospital)

THE first section of this presentation is based upon a survey of the cases of premature separation of the normally implanted placenta occurring in the Philadelphia Lying-in Hospital during the twelve-year period from 1934 to 1945. Cases presenting this complication prior to the twenty-eighth week of pregnancy have been excluded from the study.

TABLE I. INCIDENCE OF PREMATURE SEPARATION OF THE PLACENTA

Philadelphia Lying-in 1934-1945 (inclusive)

Total number of deliveries	28,288
Number of cases of abruptio	113
Incidence of abruptio	1 in 250

The wide variation in the recorded incidence of abruption of the placenta can be accounted for by the strictness of the criteria which one establishes for the inclusion of cases. For the purpose of this study we have excluded all cases in which there was no clinical evidence of separation. An almost equal number was eliminated in which the condition was recognized only after delivery of the placenta by the discovery of small retroplacental clots, or minute organized areas of separated placental tissue. The group of 113 cases is composed, therefore, only of those presenting one or more of the following typical clinical manifestations of placental separation: continuous uterine pain, tenseness and tenderness of the uterus, evidence of intrauterine hemorrhage, or frank external bleeding.

TABLE II. ETIOLOGICAL FACTORS IN PREMATURE SEPARATION

	NUMBER	PER CENT
Toxemia of late pregnancy	54	48
Unknown	59	52
Total	113	100

Hypertension and/or albuminuria were found in almost one-half of the entire group, and in many of those in which the etiology is recorded as unknown, rather typical symptoms such as abnormal gain in weight and edema, strongly suggested the presence of toxemia. A pre-existing hypertension in many others may have been masked by a fall in blood pressure incident to hemorrhage. A definite history of trauma was elicited in only one instance; in this patient the co-existence of toxemia was a more likely cause of the separation.

*Read by invitation before the South Atlantic Association of Obstetricians and Gynecologists February 8, 1947, at Savannah, Georgia.

TABLE III. TIME OF OCCURRENCE OF ABRUPTIO

	CASES	PER CENT
Before labor	63	56
During labor	50	44
Total	113	100

TABLE IV. SEVERITY OF CASES OF ABRUPTIO

Mild	35
Moderate	39
Severe	39
Total	113

The mild cases were those occurring, almost without exception, during labor, manifested by somewhat more than usual bleeding, some increase in uterine tension, and, occasionally, evidences of slight or moderate fetal distress. In this group there were no maternal deaths. The severe cases were those in which there was evidence of a large concealed or external hemorrhage.

TABLE V. METHOD OF DELIVERY IN ABRUPTIO; 1934-1945

		CASES	PER CENT
Vaginal Delivery		47	42
Forceps	23		
Spontaneous	19		
Podalic version	1		
Breech extraction	4		
Abdominal Delivery		66	58
Cesarean section	62		
Porro cesarean	4		
Total number of cases		113	100

The choice of treatment in cases of abruptio is dependent upon several factors, chief among which are the severity of the symptoms, the general condition of the patient, whether or not the patient is in labor, and, most important, the degree of cervical dilatation. In dealing with the milder degrees of separation occurring in the course of labor, in which neither the mother nor the baby present evidence of distress, it is rarely necessary to interfere with the normal course of labor. This is evidenced by the fact that of the forty-seven patients with mild or moderate degrees of separation who were delivered by forceps, breech extraction, or spontaneously, only one patient died; in this case acute hepatitis was primarily responsible for death. As seen in the following table, three-fourths of the patients whose abruption occurred during labor were delivered vaginally.

TABLE VI. METHOD OF DELIVERY ACCORDING TO ONSET OF LABOR

	CASES	PER CENT
Abruptio during labor	50	
Cesarean section	12	24
Vaginal delivery	38	76
Abruptio before labor	63	
Cesarean section	54	86
Vaginal delivery	9	14

On the other hand, the more urgent cases, because of extreme loss of blood and shock require that the uterus be emptied by the quickest method compatible with safety to the mother. Not until the uterus is empty can firm contraction

of the uterus close the bleeding sinuses of the placental site. If, therefore, the separation is of major degree and if the patient cannot be immediately and safely delivered by simple measures from below, we feel that cesarean section is the treatment of choice. In the more severe cases cesarean section is done in the interest of the mother, even though the child is known to be dead. Before instituting any procedure for delivery, it is imperative that the patient be treated for shock and that lost blood be adequately replaced by transfusion. A fine point of judgment is required in determining how long to postpone operative measures while awaiting reaction from shock. No arbitrary rules can be enunciated, as every case must be individually considered.

TABLE VII. MATERNAL MORTALITY FROM ABRUPTIO; 1934-1945

	NUMBER	PER CENT
Number of cases of abruptio	113	
Number of maternal deaths from abruptio	2	1.8

TABLE VIII. MATERNAL MORTALITY ACCORDING TO METHOD OF DELIVERY; 1934-1945

Vaginal delivery (Patient died of acute hepatitis)	1 death in 47 cases	2.1%
Cesarean section	1 death in 66 cases	1.5%
Total maternal mortality	2 deaths in 113 cases	1.8%

Removal of the uterus was deemed advisable in but four of the 66 patients who were treated by cesarean section. We do not remove the uterus simply because of its darkened appearance from extravasation of blood, but only if it fails to contract following its evacuation. There was no fatality incident to this procedure.

Following delivery, attention must be given to the likelihood of postpartum hemorrhage. Many of these uteri fail to remain firmly contracted, and a relatively small amount of bleeding will be poorly tolerated by the patient who has already suffered a considerable loss of blood. Firm packing of the uterus and vagina is urgently indicated, on the least provocation, as is also the intravenous administration of oxytocics.

TABLE IX. GROSS FETAL MORTALITY FROM ABRUPTIO; 1934-1945

Total number of cases of abruptio		113	
Total number of fetal deaths		39	35%
Stillborn	19		
Neonatal deaths	20		
(19 of the 39 dead babies weighed less than 4 pounds)			
Corrected fetal mortality			21%

Since fully one-fourth of the babies were dead in utero at the time of admission to the hospital, and since nineteen of the babies weighed less than four pounds, the total uncorrected mortality rate of 35 per cent is better than had been anticipated. There is no doubt, however, that this could be substantially reduced by more prompt recognition of the significance of the symptoms on the part of both patient and physician.

The following are brief summaries of the two fatal cases of abruptio placentae.

CASE 1.—A toxic patient had profuse bleeding and signs of abruptio at the eighth month, about four hours after the onset of labor. She was delivered of a six-pound stillborn child by forceps. Free postpartum bleeding continued

despite packing of the uterus and vagina. A total of 2,250 c.c. of whole blood and infusions of glucose were given. The patient died six days after delivery, of acute hepatitis as proved at necropsy. This death was considered in staff conference as nonpreventable.

CASE 2.—An 18-year-old Negro patient, whose early prenatal course was eventful, was admitted in mild pre-eclampsia at full term. The fetal heart sounds could not be heard. Her cervix was not dilated and her pains were irregular until one hour after admission. At that time her membranes ruptured spontaneously; she had a moderate amount of external bleeding. One hour later she had definite evidence of concealed hemorrhage and cesarean section was elected. In the hour and a half elapsing before operation, her blood pressure fell from 140/90 to 80/50. Because of this, an infusion of plasma was started simultaneously with the operation. A stillborn child and the completely separated placenta, along with 2,000 c.c. of blood were evacuated from the uterus. The uterus was packed and routine closure was performed. A transfusion of 500 c.c. of whole blood was given, but the patient failed to react and died one hour after completion of the operation. This death was reviewed in staff conference and was considered to have been preventable in that shock was not adequately treated before operation and that replacement of blood loss was insufficient.

Summary

Review of this series of cases of premature separation of the placenta will, we believe, establish the following principles concerning this complication:

1. Since toxemia of pregnancy is thought to be a potent etiological factor in approximately one-half of such cases, good prenatal care offers much in the way of prevention of abruptio.

2. No patient with hypertension should be allowed to be far from expert obstetric care.

3. Early recognition by both patient and physician, of the significance of antepartum hemorrhage is imperative.

4. In a decision to delay interruption of pregnancy in toxemia patients until the time of greater viability of the child, consideration must be given to the possibility of premature separation.

5. If the case be one of mild degree, the conduct of labor may be unaltered except for increased vigilance on the part of the attendant.

6. In the more severe cases the best interests of both mother and baby are served by as prompt evacuation of the uterus as is compatible with safety.

7. Manual dilatation of the cervix and other traumatic procedures for delivery have no place in the elective treatment of abruptio.

8. Treatment for shock and replacement of blood before instituting measures for delivery will greatly decrease the operative risk.

9. Prompt replacement of blood following delivery decreases not only the immediate danger, but also lessens the incidence of puerperal infection.

Placenta Previa

The second section of this presentation consists of a study of our experience with cases of placenta previa at the Philadelphia Lying-in Hospital from 1934 to 1945. We have included in this survey only those cases occurring beyond

the twenty-eighth week of pregnancy in which the diagnosis was definitely established by feeling the placenta through the cervix, its visualization by x-ray studies, or by confirming its low attachment at the time of cesarean section. By observance of these strict criteria, a large number of cases of mild painless bleeding were eliminated, even though it is quite likely that a relatively low implantation of the placenta existed in many of these cases.

TABLE XI. INCIDENCE OF PLACENTA PREVIA; PHILADELPHIA LYING-IN HOSPITAL 1934-45 (INCLUSIVE)

Total number of deliveries	28,288
Number of cases of placenta previa	92
Incidence of placenta previa	1 in 307

TABLE XII. TYPES OF PLACENTA PREVIA

	NUMBER
Lateral	25
Marginal	33
Central	20
Not stated	14
Total	92

As seen in the foregoing table the marginal type, in which the placenta covered only a portion of the internal os, was most frequently encountered. Next in order of frequency were lateral and central implantations.

TABLE XIII. METHODS OF DELIVERY IN PLACENTA PREVIA

		CASES	PER CENT
Vaginal delivery		17	19
Forceps	5		
Spontaneous	6		
Version and extraction	3		
Breech extraction	2		
Braxton-Hicks version	1		
Cesarean section		75	81

The choice of treatment in placenta previa is dependent upon the following factors: the severity of hemorrhage, the degree of shock, the location of the placenta, the viability of the child, its presentation, and, most important of all, the amount of cervical dilatation.

If the bleeding occurs during labor, and the placenta is marginal or lateral, and the presentation is polar, rupture of the membranes will most often allow the presenting part to make sufficient pressure on the separated placenta to control the bleeding. In such instances we allow labor to proceed to spontaneous delivery or to a low forceps application. If the cervix is completely dilated and if the baby is small, version and extraction may occasionally be the procedure of choice, except in the central type of implantation. Because of the potent danger of deep laceration of the cervix extending into the placental site, we feel that the manual dilatation of the cervix is strictly contraindicated.

Braxton-Hicks version, while occasionally a lifesaving measure for the mother under emergency conditions, is, we believe, best reserved for those cases of marginal and lateral placenta previa in which the child is dead or not viable.

By following these principles, we were able to deliver seventeen of our patients by the vaginal route, with no maternal mortality.

In seventy-five of our cases, cesarean section was performed. If the bleeding is profuse and the cervix is closed, we feel that the interests of both mother and child are best served by this procedure. Regardless of the amount of cervical dilatation cesarean section is done in practically every case of central placenta previa and in most instances of malpresentation.

TABLE XIV. MATERNAL MORTALITY FROM PLACENTA PREVIA; 1934-1945

Number of cases of placenta previa	92	
Number of maternal deaths from placenta previa	2	(2.2%)

TABLE XV. MATERNAL MORTALITY ACCORDING TO METHOD OF DELIVERY; 1934-1945
(PLACENTA PREVIA)

		PER CENT OF MORTALITY
Vaginal delivery	0 deaths in 17 cases	0.0
Cesarean section	2 deaths in 75 cases	2.7
Total maternal mortality	2 deaths in 92 cases	2.2

As seen in the above table, there were no deaths among the seventeen patients in whom the amount of cervical dilatation and other favorable factors permitted vaginal delivery. Unfortunately, a relatively small number were found amenable to such simple measures.

Following are the summaries of the two fatal cases of placenta previa:

CASE 1.—Cesarean section was done for central placenta previa under gas, oxygen, ether anesthesia. Bleeding was not profuse. The patient was obese (232 pounds), and was not in shock. She died of bronchopneumonia on the fifth postoperative day. The baby lived. This death was considered nonpreventable in our staff conference.

CASE 2.—The patient, with history of slight painless bleeding for six weeks, had a medical induction of labor, including three minims of pitocin. She immediately began to bleed steadily but not profusely. Cesarean section was done because of marginal placenta previa with only two fingers dilatation of the cervix. Profuse hemorrhage occurred during anesthesia. The baby lived. The mother failed to react to infusion during, and transfusion after operation. She died of shock and hemorrhage one and one-half hours later. This case was considered preventable in our staff conference in that shock was not adequately treated, a sufficient amount of blood was not given, and pitocin was used in the induction of labor.

TABLE XVI. GROSS FETAL MORTALITY ACCORDING TO METHOD OF DELIVERY
(PLACENTA PREVIA)

		PER CENT OF MORTALITY
Vaginal delivery	9 deaths in 17 cases	53
Cesarean section	15 deaths in 75 cases	20
Total fetal mortality	24 deaths in 92 cases	26
(Nine of the 24 dead babies weighed under 4 pounds)		
Corrected fetal mortality		18.5

Intrauterine asphyxia was presumably responsible for eleven fetal deaths and was, no doubt, a contributory cause in all of them. Prematurity was the next most frequent factor, as nine of the twenty-four babies who died weighed less than 4 pounds.

Our experience has resulted in our adoption of certain principles in the management of placenta previa.

1. Accurate diagnosis of the cause of bleeding is essential. A cautiously performed vaginal examination may reveal that the bleeding is due to a cervical polyp, an erosion, or, rarely, a cervical carcinoma, rather than to a placenta previa. Examination, however, entails the danger of sudden profuse bleeding as well as the risk of infection. It is our invariable rule that no patient suspected of placenta previa be examined until the operating room is ready for both vaginal and abdominal delivery.

X-ray studies by the "soft tissue" technique have in the past few years been a valuable aid in localization of the placenta. By this method the normally situated placenta is well visualized in practically all cases; the low-lying placenta is hidden by the pelvic bones. Finding the placenta high in the uterus is definite evidence against placenta previa; failure to visualize it indicates that the placenta is probably, but not necessarily, located in the lower uterine segment. The technique is, therefore, dependable only in ruling out, rather than positively diagnosing, placenta previa. This method of study is applicable obviously only to those patients whose bleeding has almost or entirely ceased. Our experience with the cystogram technique of Ude and Urner has led us to doubt its clinical value.

2. Treatment of shock and replacement of blood by transfusions of whole blood or plasma are essential before instituting procedures for delivery. Indeed, the patient should not be examined until she has reacted, because of the danger of additional hemorrhage from digital dislodgement of the placenta.

3. Expectant treatment of patients with placenta previa in the hope of bringing the child to greater viability is never justified unless the patient remains in the hospital throughout the remainder of pregnancy.

4. The method of delivery is almost wholly dependent on the status of the cervix. Because of the danger of profuse hemorrhage from the vessels of the placental site and the added risk of infection, manual dilatation of the cervix and forcible vaginal delivery have no place in the treatment of this condition. If the cervix is dilated and the placenta previa is only partial or marginal, rupture of the membranes will allow the presenting part to make pressure on the placenta sufficient to stop the hemorrhage. Under similar conditions version and extraction are indicated only if the cervix is *completely* dilated. Braxton-Hicks version, we feel, should be utilized only in those cases in which the baby is dead or nonviable and in which the cervix is partially dilated. While it is undoubtedly a valuable means of saving maternal life under emergency conditions, it entails almost certain sacrifice of the child.

The hydrostatic bag possibly has its place in the treatment of certain cases of marginal and lateral placenta previa but several instances of continuing intrauterine hemorrhage following its insertion have resulted in our abandonment of this procedure.

In all cases in which the cervix is not dilated, in all cases of central placenta previa regardless of the cervical dilatation, and in those of malpresentation

of the fetus, cesarean section is the safest, and therefore the most conservative form of treatment.

5. The use of an oxytocic intravenously immediately on completion of the second stage of labor, and firm packing of the uterus and the vagina after expulsion or removal of the placenta will considerably lessen the danger of postpartum hemorrhage. In most instances packing the uterus after cesarean section for placenta previa is adviasble.

6. Blood transfusions are indicated following delivery to combat anemia and to improve the patient's resistance to infection.

Summary

1. A series of 113 cases of premature separation of the placenta is reported, with a maternal mortality rate of 1.8 per cent.

2. A series of 92 cases of placenta previa is reported, with a maternal mortality rate of 2.2 per cent.

3. Methods of management of these two complications are discussed.

807 Spruce Street

THE ELECTIVE USE OF KIELLAND FORCEPS IN MANAGEMENT OF OCCIPITOPOSTERIOR AND OCCIPITOTRANSVERSE POSITIONS

LEE M. MILES, M.D., F.A.C.S., ALBUQUERQUE, N. MEX.

(From the Department of Obstetrics and Gynecology of the Lovelace Clinic)

MANAGEMENT of labor in occipitoposterior and transverse positions of the fetal head has been in a static stage for many decades. The utmost of conservatism still prevails in the teaching and in the literature dealing with this subject. Whether the writer favors manual rotation to an anterior position with subsequent delivery with conventional forceps as advocated by Danforth[1-2]; rotation of the head by "key in lock" multiple application of forceps; or some modification of the Scanzoni maneuver (Danforth[3]); or the use of Barton forceps (Langman and Taylor[4]); or the Kielland forceps (Kushner and Wahrsinger[5]); all agree that before any attempt to terminate labor full dilatation of the cervix with strong labor pains should have occurred for two hours or more, or that there shall be obvious signs of either fetal or maternal distress or both.

In this presentation I offer a critical analysis of 2,601 consecutive deliveries of private patients in which Kielland forceps were used in 547 instances of occipitoposterior and transverse positions. In the great majority of these 547 instances the forceps were used as an elective procedure to rotate and deliver the fetal head as soon as, or shortly after, full dilatation was obtained.

Occipitoposterior and transverse positions of the fetal head occur frequently, according to Bacon,[9] 30 per cent of all vertex presentations; Danforth,[1-2] 26 per cent; and Calkins,[21] 48.3 per cent. Spontaneous rotation to an anterior position does occur frequently depending on a number of factors, the size of the fetal head and the size of the pelvis, the length of time allowed for molding of the head, the strength of the forces of labor and the internal contour of the pelvic passage. Much light has been shed on this last factor by the work of Caldwell and Moloy[6] and Caldwell, Moloy, and D'Esopo[7-8] in describing by means of extensive x-ray studies the type of pelvis in which posterior and transverse positions are likely to persist.

Kielland Forceps

American medical literature is not replete with articles pertaining to the use of Kielland forceps. Although Kielland presented his forceps and described in detail his method of using the instruments in 1915, it was not until 1924 that Greenhill[10] made a thorough study of collected reports from European literature. Since then sporadic articles have appeared in American medical journals.[11-19] Most of these articles are brief accounts of the use of Kielland forceps in a small series of cases. Kushner and Wahrsinger[5] and Langman and Taylor[4] presented excellent statistical studies of significantly large series of cases.

Lengthy descriptions of the forceps themselves and the method of their use are not necessary. There are, however, a few points that will bear emphasis.

With two exceptions, the instruments should always be applied in the original Kielland manner. This consists in first introducing the anterior blade well into the uterine cavity, and then rotating it into apposition with the fetal head. This rotation should cause the tip of the blade to describe an arc in a "clockwise" direction when the occiput is directed to the right side of the mother's pelvis, and "counter clockwise" when left occipitoposterior or transverse position of the head is present. In actual use two fingers of the left hand are inserted into the vagina and between the cervix and the fetal head. The head should not be disengaged or disturbed in any manner. The tip of the anterior blade, pointing upward, is then inserted between the fingers in the vagina and the cervix. Frequently as the blade passes into the uterine cavity there is encountered a definite resistance. If the examining fingers are thrust upward this resistance is found to be due to a constriction of the uterine muscle at the level of the junction of the cervix with the uterine musculature. Johnson[20] has described this condition and calls it "temporary or functional contraction ring." If delivery is too long delayed, this "functional" contraction ring may become the pathologic contraction ring. When this resistance is encountered the handle of the forceps is elevated and the tip of the blade passes readily into the uterine cavity, where it can be rotated and applied to the fetal head. The posterior blade is then inserted and articulated with the anterior blade.

The two exceptions to this method of insertion of the blade are: first, when a true contraction ring is present it is dangerous to attempt the insertion of the blades by the rotation method and in this case the "wandering" manner of insertion is advisable; second, when the head is low in the pelvis and the occiput is directly posterior the blades are applied to the sides of the fetal head exactly as with classical forceps, keeping the markers on the handles directed toward the occiput. The head may then be rotated without difficulty and delivered with a single application of the forceps.

Rotation of the head may be accomplished by one of three procedures:

1. *Rotation without traction.* If the head is lying in the plane of greatest pelvic diameter, gentle rotation of the handles in a straight line and not with a sweeping movement, will usually suffice to bring the occiput to an anterior position.

2. *Rotation with traction.* If the method described above does not readily produce rotation, traction with rotation simultaneously applied will produce rotation accompanied by descent of the head.

3. *Disengagement of the head with rotation above the pelvic brim.* This would appear to be a dangerous and radical procedure. However, the cephalic curve of Kielland forceps fits the fetal head so accurately that thrusting the head up and out of the pelvis does disengage the head from the forceps. The head is readily rotated to an obliquely anterior position and traction with the resulting descent of the head and further rotation brings the head to the desired anterior position and delivery is effected.

It is, of course, understood that there is no cephalopelvic disproportion existing that precludes the possibility of delivery through the vagina. Traction for delivery should be applied in the direction naturally taken by the handles

of the forceps. Too early elevation of the handles causes deflexion of the head with the result that too great force is necessary to bring about delivery and the more unfavorable diameter of the head as it is forced through the birth canal may result in severe lacerations of the outlet.

Material

The material for this analysis consists of 2,588 consecutive private patients delivered at St. Joseph's Hospital and at the Southwestern Presbyterian Hospital. Neither of these hospitals has an intern or resident staff. Labors and deliveries were conducted by myself with the assistance of a very efficient nursing staff. In order to have the results uniform and not subject to personal variation, the work of my associates is not included in this report. With necessary variations to suit individual cases, a definite routine as regards nutrition, elimination, observation and medication was carried out in all cases. All labors were conducted by vaginal examinations preceded in each instance by a vaginal instillation of 15 c.c. of a 5 per cent aqueous solution of Mercurochrome. In this series 2,588 mothers were delivered of 2,601 babies, twins having occurred twenty-six times. Table I shows the distribution of these cases by presentation of the fetus.

TABLE I

PRESENTING PART	NUMBER	PER CENT
Vertex	2,499	96.07
Breech	93	3.60
Shoulder	7	.26
Face	2	.07
Total	2,601	100.00

Table II breaks down these figures still further to show the method of delivery.

TABLE II

TYPE OF DELIVERY	NUMBER	PER CENT
Breech	93	3.60
Version and extraction	26	1.00
Cesarean section	78	2.99
Decapitation	1	.038
Craniotomy (hydrocephalus)	1	.038
Occipitoanterior (spontaneous or outlet forceps)	1,808	69.51
Occipitoposterior (Scanzoni or key in lock)	7	.26
Occipitoposterior (manual rotation)	9	.346
Occipitoposterior (delivered as such)	31	1.19
Occipitoposterior (Kielland forceps rotation)	547	21.03
Total	2,601	100.00

These 547 cases in which Kielland forceps were used for rotation and delivery of fetuses presenting in occipitoposterior position were comprised of two groups of patients. Thirty-six of these patients were referred to me for delivery after attempts at delivery, including attempts at forceps delivery, version and full doses of pituitrin, had failed. Some of these women had traveled long distances, one came over 200 miles. These women all presented the classical findings referred to as the customary indications for operative intervention. These

patients had all been in labor for hours without progress, the mothers were in a state of near exhaustion, the fetal heads were all extremely molded, and the fetuses were all in evident distress if not already dead. This group contributed largely to the number of morbid mothers and to stillborn infants and to neonatal deaths.

The remaining 511 cases consisted of mothers who were under my care from early in pregnancy through labor. In this group of patients I did not set any arbitrary time limit before which operative assistance* was contraindicated, such as two or more hours of hard second stage labor, nor did I wait for signs of maternal or fetal distress or both. When the cervix was fully dilated and the head deeply engaged in the pelvis, the patient was taken to the delivery room and prepared for delivery. Under anesthesia the Kielland forceps were applied in the original manner and the head rotated and delivery effected. I do not consider it to be necessary or advisable to remove the Kielland forceps and apply conventional instruments for the actual delivery.

Maternal End Results

Such a radical departure from the conventional indications for any procedure to assist rotation and delivery of the fetus presenting in occipitoposterior or occipitotransverse positions must be justified by the results obtained. The results are presented in Table III, showing the effect of the procedure from the maternal standpoint. The standard of morbidity used in this series is that established by the American College of Surgeons. There were no deaths from infection in the entire series. Of the patients delivered by Kielland forceps who had a febrile puerperium, seven were among those patients who were brought to the hospital after long labor and attempts at delivery made at home under anything but proper conditions. All seven had intrapartum infection before arrival at the hospital.

TABLE III

Total mothers delivered	2,588	
Total morbidity	95	3.67%
Mothers delivered other than by Kielland forceps	2,041	
Morbidity	76	3.72%
Mothers delivered by Kielland forceps	547	
Morbidity	19	3.47%

Actual causes of morbidity of the entire group were as follows: acute pyelocystitis, thirteen; acute respiratory tract infection, five; active pulmonary tuberculosis, two. All the remaining febrile reactions were considered to be puerperal in origin. There were three cases of thrombophlebitis in the entire series. *No prophylactic administration of sulfonamides or penicillin was used.* These drugs were administered on indication only and the sulfonamides were used in exactly fifty instances, and penicillin in only six cases. Total maternity mortality in the 2,588 mothers was six. In the series of 547 mothers delivered by Kielland forceps there were two deaths, neither death could be attributed to the method of delivery. One death occurred in the case of an eclamptic woman who was brought to the hospital comatose and moribund, and the other death was due to a pulmonary embolus.

Other maternal complications in this series were postpartum hemorrhage and lacerations or extensions of episiotomy incisions involving the rectum. Postpartum hemorrhage occurred in the group of 547 women delivered by Kielland forceps in six cases, or 1.09 per cent, and among the 2,041 women delivered by other means the occurrence of hemorrhage was twenty-two, or 1.07 per cent. The only complication that occurred with greater frequency in those mothers deliv-

*The terms "operative interference" and "operative intervention" should be deleted from obstetric terminology and the term "operative assistance" substituted.

ered by Kielland forceps than in the other group was laceration involving the rectum, five cases in the Kielland forceps group, and two cases in the mothers delivered by other means. In only one instance did the laceration include the sphincter muscle, the others were lacerations into the lumen of the bowel above the sphincter muscle. All were treated by immediate repair and all healed without complication. The one complete tear followed use of conventional forceps. On discharge from the hospital, and at the postpartum examination, her sphincter control was good.

From the above analysis it is evident that, as far as the mother is concerned, there is no appreciable difference in the outcome of delivery as the result of the elective use of Kielland forceps as compared with the other methods of delivery.

Fetal End Results

The object of all obstetric care is to complete the cycle of pregnancy, parturition, and puerperium with a well mother and a well baby. Table IV analyzes the results from the standpoint of fetal survival.

TABLE IV

Total births other than by Kielland forceps	2,054	
Stillbirths under 1,500 Gm.	10	0.48%
Stillbirths over 1,500 Gm.	33	1.6 %
Neonatal deaths under 1,500 Gm.	22	1.07%
Neonatal deaths over 1,500 Gm.	16	0.78%
Total births by Kielland forceps	547	
Stillbirths over 1,500 Gm.	5	0.9 %
Neonatal deaths over 1,500 Gm.	8	1.46%

Among the babies delivered by Kielland forceps there were no fetuses under 1,500 Gm. in weight. Of the five stillborn fetuses, four were badly macerated at birth. Of the eight neonatal deaths among the fetuses delivered by Kielland forceps, autopsy demonstrated three cases of anatomical conditions incompatible with life: pulmonary atelectasis one, congenital cystic kidney one, hydrocephalus and spina bifida one. Excluding these three cases of congenital deformity, the corrected neonatal mortality is 0.90 per cent. Of the five remaining neonatal deaths only one autopsy was obtained, and that showed the cause of death to be intracranial hemorrhage, and the same cause was ascribed to the other four deaths. These deaths occurred in the group of cases that would be usually classified as "indicated" Kielland forceps deliveries. In the group of fetuses delivered by the "elective" use of Kielland forceps such fetal complications as marked molding of the fetal head, caput succedaneum and cephalhematoma were almost entirely absent.

There were only six instances in which delivery could not be effected by Kielland forceps. In these six cases the forceps were successfully applied and rotation was accomplished, but traction did not result in descent of the head and the forceps were removed. Cesarean section was performed twice with good results to mother and baby, version was done four times, with good result in three. In the fourth case, not considered as safe to perform a section, the version delivery resulted in fetal injury which developed into hydrocephalus of traumatic origin and the child died at the age of 2 years.

Discussion

It is now a matter of general agreement that, as far as the mother is concerned, the skillful use of forceps under suitable conditions to effect delivery, does not affect the outcome so far as life and health are concerned. From the

maternal viewpoint, the end result of the use of forceps is that labor is shortened. In spite of a great variety of procedures aimed at decreasing the pain of childbirth, ranging from mental suggestion to continuous caudal anesthesia; in spite of a great variety of analgesic drugs, the fact remains that the *one positive thing* we can do to lessen the pain and shorten the period of suffering is to give the parturient woman the benefit of operative assistance in delivery. Is this worth while? The late Dr. Joseph B. DeLee thought it was when he advocated the routine use of forceps in the procedure for which he coined the name *Prophylactic Forceps.*

In the case of occipitoposterior positions, it is well recognized that the first stage of labor is prolonged. Not only is the first stage prolonged, but the particular character of the pains is more severe than in occipitoanterior positions. This is probably due to the fact that in most occipitoposterior positions, the cervix lies far posterior in the hollow of the sacrum and the uneven pressure on the cervix is peculiarly painful. I have shown in this series of cases in which Kielland forceps were used early in the second stage, that the procedure is devoid of danger to the mother. Kushner and Wahrsinger[5] state, "There were six cases of mitral stenosis, where the second stage was entirely eliminated. Forceps (Kielland) were applied when full dilatation was attained." If, as I have demonstrated in my study of 547 cases of the use of Kielland forceps, and as the writers quoted above admit, the early application of Kielland forceps in occipitoposterior and transverse positions is safe for the mother, and results in shortening her labor and relief of pain, it is therefore a worth-while procedure.

From the standpoint of the fetus which has had the misfortune to present itself in an occipitoposterior position, the matter of early versus late application of Kielland forceps with rotation and delivery is a matter of vital importance. Langman and Taylor[4] report 134 instances of their use of Kielland forceps with fetal and neonatal loss of twenty-one. Kushner and Wahrsinger[5] report 200 cases with a fetal and neonatal loss of fourteen. In my series of 547 deliveries with Kielland forceps, the fetal and neonatal loss was thirteen. It is not my purpose to compare my skill in the art of Kielland forceps application with these other writers. It is my intention to point out that the essential difference in results is directly due to early delivery before damage has been done to the fetus as the direct result of the forces of labor. In none of my cases was an arbitrary "watching and waiting" time required. In the great majority of my own cases, forceps were applied shortly after full dilatation was attained. The disastrous results to the fetus in my series were due to delay. It is my firm conviction that had delivery been effected earlier in labor in all instances, the fetal loss would have approached zero.

Summary and Conclusions

1. A critical study of 547 deliveries with Kielland forceps out of a total of 2,601 consecutive deliveries is presented.

2. Maternal morbidity and maternal complications were not increased by the procedure of early application of Kielland forceps.

3. Two maternal deaths occurred in this series of 547 deliveries, neither of which could be attributed to the method employed in delivery.

4. The total fetal loss was thirteen—net loss ten.

5. The best results from the fetal standpoint were in those instances in which Kielland forceps were applied early in the second stage of labor.

6. The early application of Kielland forceps is accomplished with less difficulty and with much less occurrence of damage to either mother or baby than the application late in the second stage of labor.

7. Kielland forceps are ideal for dealing with occipitoposterior and transverse positions.

8. The use of Kielland forceps under suitable conditions as an elective procedure is recommended in dealing with these cases.

My appreciation is tendered to Sister Williamana, Medical Librarian of St. Joseph's Hospital, and to Miss Lillian Henningson, Medical Librarian of the Southwestern Presbyterian Hospital, for their assistance in making these records available for study.

References

1. Danforth, W. C.: Am. J. Obst. & Gynec. **23**: 360, 1932.
2. Danforth, W. C.: Am. J. Obst. & Gynec. **28**: 756, 1934.
3. Danforth, D. N.: Illinois M. J. **90**: 212, 1946.
4. Langman, Louis, and Taylor, Howard C., Jr.: Am. J. Obst. & Gynec. **52**: 773, 1946.
5. Kushner, J. Irving, and Wahrsinger, Philip B.: Am. J. Obst. & Gynec. **52**: 110, 1946.
6. Caldwell, W. E., and Moloy, H. C.: Am. J. Obst. & Gynec. **26**: 479, 1933.
7. Caldwell, W. E., Moloy, H. C., and D'Esopo, D. A.: Am. J. Obst. & Gynec. **28**: 824, 1934.
8. Caldwell, W. E., Moloy, H. C., and D'Esopo, D. A.: Am. J. Obst. & Gynec. **30**: 763, 1935.
9. Bacon, C. S.: J. A. M. A. **86**: 465, 1926.
10. Greenhill, J. P.: Am. J. Obst. & Gynec. **7**: 349, 1924.
11. Gaylor, W. C.: J. Missouri M. A. **23**: 63, 1926.
12. Goldberg, Simon P.: M. J. & Rec., May 16, 1928.
13. Jarcho, Julius: Am. J. Obst. & Gynec. **10**: 1, 1925.
14. King, E. L.: New Orleans M. & S. J. **80**: 630, 1928.
15. Patterson, W. R.: Canad. M. A. J. **28**: 177, 1926.
16. Bloss, J. R. West Virginia M. J. **27**: 489, 1931.
17. Scadron, S. J.: Surg., Gynec. & Obst. 697 (May), 1925.
18. Harrar, James A.: Am. J. Surg. **35**: 391, 1937.
19. Rucker, M. Pierce: Virginia M. Monthly **66**: 653, 1939.
20. Johnson, Herman W.: Am. J. Obst. & Gynec. **52**: 74, 1946.
21. Calkins, L. A.: Am. J. Obst. & Gynec. **38**: 993, 1939.

A MULTIPLE SULFONAMIDE THERAPEUTIC MEASURE IN THE POSTOPERATIVE CARE OF THE CERVIX AND VAGINA*

A. HERBERT MARBACH, M.D., F.A.C.S., PHILADELPHIA, PA.

(From the Jewish Hospital)

IN RECENT years the knowledge of vaginal physiology[1-9] has increased tremendously. In diseased states of these organs we attempt to redirect pathologic variables to a state of normal physiologic function, with judicious expedition, through the utilization of chemotherapeutic principles. Medicine's recent advances in chemotherapy have been remarkable. With these newly applied principles, the healing times in vaginal and cervical operations can be decreased considerably.

In postoperative vaginal and cervical conditions there exist four main physiologic imbalances tending to delay prompt healing:

1. The patient's vaginal flora changes, from Grade 1 to Grades 2 and/or Grade 3.
2. The pH approaches neutrality.[10-13] There is a progressive swing of the pH toward that favoring the more optimal growth of secondary bacterial invaders.
3. The epithelial strata are destroyed or decreased in height. This is related to catabolic excretions of low grade pathogenic bacteria hostile to superficial mucosal cells by virtue of exotoxins and other unfavorable excretory substrates.
4. The glycogen availability of the tissue is decreased. As the upper mucosal layers, containing the greater amount of this polysaccharide, are destroyed the glycophilic needs of the secondary bacterial invaders become more adequate. A vicious circle is thus developed. Too, we are aware the acidosis of anesthesias exert a direct glycogenolytic influence upon the body tissues.[24] All these depriving variables contribute to the continuing depletion of normal glycogen content.

One logical approach to decrease the vaginal discharge and restore normal physiological mucosal balance was to suppress the secondary bacterial invaders. It is principally these saprophytic invaders which are responsible for the changes in the delicate physiologic equalization.

The role of the sulfonamide derivatives was considered to represent one possible approach toward the assistance of the normal reparative process, provided the formulation of such therapy considered such additional requisites to tissue repair than only the control of bacterial invaders. It is known that sulfonamide derivatives control secondary bacterial invaders at optimally specific bacteriostatic ranges. Cowles[14] demonstrated that the maximal bacteriostatic action for a given sulfonamide half dissociation constant was obtained within its paralleling specific pH range. A further indication for the

*Presented before the Philadelphia Obstetrical Society, Jan. 3, 1946.

use of more than one sulfonamide is found in Lehr's[15] studies of inhibition of drug precipitation in the urinary tract by sulfonamide mixtures. It was possible to obtain such a mixture of sulfa derivatives whose optimal pKa's and parallel pH's would fall within the maximal and minimal pH range encountered during the course of healing of cervicovaginal operative lesions. This hypothesis was subjected to a carefully controlled laboratory study prior to initiation of the present clinical study.

The enhancement of sulfonamide activity by urea and related compounds has been demonstrated by several investigators.[16-20] This action depends on the facts that (a) bacteria, especially Gram-negative organisms, are killed or inhibited by urethane and carbamates themselves; (b) urethanes and their derivatives have a competitive action on para-aminobenzoic acid which is inhibitory to sulfonamides.

The problem of application of these drugs to the surgical area was considered. In view of the wide but convoluted epithelium of the vaginal rugae to be covered, as well as the irregular crevices and interstices occasioned by operative procedure, it was necessary to select a base which would adhere to the mucosal surfaces as well as be water-dispersible and absorptive in nature.[21] The dosages of sulfa derivatives was determined upon a molecular equivalent basis that no more than 10 per cent of the formula were sulfacrystals by weight. This percentage of the actual principles was distributed as follows: 3.42 per cent sulfathiazole, 2.86 per cent acetyl-sulfanilamide, 3.70 per cent benzoyl-sulfanilamide and 1 per cent urea peroxide.* Animal studies revealed nontoxicity and no untoward side effects. Absorption rates through intact and disrupted mucosal surfaces were performed. Rabbits weighing approximately 4.0 kg. were used in the study. Three grams of cream were applied over a shaved area upon the dorsum. Hourly blood levels were determined. The peak of absorption, at the fourth hour, was 2.50 mg. per cent in the median instance. The value never exceeded 4.0 mg. per cent in any case. Absorption of the topically applied multiple sulfa cream was rapid, reaching a peak within four hours and disappearing almost entirely from the blood within twenty-four hours. The blood concentration of the total sulfonamides was below usual sulfonamide values, rising to less than 3 mg. per 100 c.c. of whole blood at any time.

Blood levels in rabbits were determined similarly after vaginal application of 3.0 Gm. of cream. The peak blood level, at five hours, was found to be 1.87 mg. per cent or 0.35 per cent per kg. body weight. The first 25 humans in this series whose blood sulfa concentrations were determined yielded only traces, several determinations rising between 0.2 to 0.4 mg. per cent. It was obvious, therefore, that the preponderant sulfonamide activity was available to the mucosal surfaces in immediate contact.

Controlled tissue tolerance tests were carried out on albino female rats. The animals were sacrificed at varying times and histologic sections of the vagina, cervix, kidneys, and liver revealed no abnormal changes. Allergic and

*The multiple sulfa cream used in this study was the Triple Sulfa Cream prepared and furnished by the Ortho Research Foundation, Raritan, New Jersey.

sensitization sulfonamide studies were determined by testing twenty-three human subjects with patch tests. No sensitivity was observed in any instance, again indicating major sulfa activity at site of application rather than systemic in action.

In Vitro Bacteriology Evaluations

Bacteriologic tests in vitro were then carried out, using the agar cup procedure. Two-tenths of a cubic centimeter of an eighteen-hour broth culture of *Staphylococcus aureus* was inoculated into approximately 20 c.c. of heart infusion agar adjusted to pH 4.6, 5.2 and 7.0. The multiple sulfa cream preparation was enclosed in a glass ring of 1.5 cm. in diameter and placed on top of the solidified inoculated agar. The plates were then incubated for twenty-four hours at 37° C. The zone of inhibited growth was measured in mm. as follows:

at pH 4.6 —11 mm. zone
pH 5.2 —11 mm. zone
pH 7.04—12 mm. zone

The results obtained in these experiments, as a whole, exhibited consistently clear-cut zones of bacteriostasis at the specific pH levels.

In view of our desire to evaluate multiple active sulfonamide principles upon postoperative sites, it was deemed advisable to determine the sterility of the preparation itself. The following method was used: one-tenth gram samples were taken aseptically from a portion of a tube near the orifice and again at a point approximately halfway down the tube. These amounts of the sulfa cream were placed in duplicate tubes of thioglycollate culture medium containing three different amounts of para-aminobenzoic acid. The amounts of P.A.B.A. were so adjusted in the three series that the ratio of sulfonamide to P.A.B.A. were 10/1, 100/1, 1000/1. The thioglycollate medium provided optimal culture conditions for both aerobes and anaerobes. After seventy-two hours incubation at 37° C. subcultures were made into homologous thioglycollate medium containing the same amounts of P.A.B.A. After a second incubation period of seventy-two hours, the subcultures were observed for evidence of gross bacterial populations, and the clear tubes were recorded as containing no live bacteria. All negative tubes were incubated nine days before final judgment was made. These negative tubes were then inoculated with *Candida albicans* and *Clostridium sporogenes* to determine whether or not either a pathogenic fungus or an anaerobe, if present in the original multiple sulfa cream, would have grown in the test culture medium. In addition, at the time the original test was set up, control tubes of thioglycollate medium containing the same amounts of P.A.B.A. were inoculated also with *Staphylococcus aureus.*

Duplicate samples from eight different batches of cream were tested. None were found to contain live bacteria or spores detectable by the method described above. All control tubes developed high bacterial populations and all of the negative tubes which were inoculated with *Candida albicans* and *Clostridium sporogenes* likewise supported good bacterial and fungus growth, demonstrating the validity of the test method. It was therefore concluded that the multiply-derived sulfa cream was sterile as prepared pharmaceutically.

The antiseptic action of the cream was investigated in order to gain information regarding its in vitro action against a variety of organisms which might be encountered in wound infections. The following bacteria were used: *Bacillus anthracis, Staphylococcus aureus, Bacillus subtilis, Streptococcus vaginalis, Streptococcus hemolyticus, Group A; Streptococcus hemolyticus, Group D; Escherichia coli, Clostridium tetani, Clostridium perifringens* and *Pseudomonas aeruginosa.* One cubic centimeter of the specially developed sulfa cream was seeded with 0.1 c.c. of a twenty-four or forty-eight hour culture of the test

organism and stirred with a sterile glass mixer for two minutes. Subcultures were then made into thioglycollate medium containing the three above-mentioned concentrations of P.A.B.A. at five, ten, fifteen, thirty, and sixty minutes, and twenty-four hours. The subcultures were incubated for seven days. Gram-stained smears were prepared from the tubes at the critical exposure times, to make certain that the bacteria found were those used in the inoculum. All negative subcultures were again subcultured into thioglycollate broth and observed an additional seven days. All tests were run in duplicate. Two types of controls were set up: (a) the test organisms were inoculated directly into media containing three concentrations of P.A.B.A.; (b) the multiple sulfa cream direct from tubes was inoculated in the same medium in order to further check its original sterility.

The results of these tests are shown in the following table:

TABLE I. THE ANTISEPTIC ACTION OF A MULTIPLE SULFA CREAM

TEST ORGANISM	KILLING TIME
Bacillus anthracis	5 min.
Pseudomonas aeruginosa	5 min.
Bacillus subtilis	5 min.
Streptococcus vaginalis (hemolytic)	5 min.
Staphylococcus aureus	30 min.
Escherichia coli	60 min.
Clostridium perifringens	30-60 min.
Clostridium tetani	60 min.
Streptococcus hemolyticus, A	1-18 hr.
Streptococcus hemolyticus, D	1-18 hr.

All control cultures gave luxuriant growth. No evidence of bacterial growth was observed in tubes receiving the cream alone.

It was concluded that the cream destroys a wide variety of pathogenic organisms of the types commonly found in surgical wounds. The killing time in all cases was brief enough to insure the destruction of these organisms during the period of time in which a special sulfa cream would be expected to remain on the wound site.

With this experimental background, and a working hypothesis of goals we hoped to attain physiologically and therapeutically, we initiated clinical evaluations on postoperative patients in whom the mucosal continuity of some area of the lower genital tract had been broken. Our previous experience with such cases was that for a period of five to six weeks following conization, vaginal hysterectomy, and vaginal plastic operations there existed vaginal discharge, greenish-brown to yellowish-green in color, malodorous in some, and moderately profuse in amount. Upon inspection of the operative sites, particularly those involving the cervix uteri, a gray-green membrane covered the areas, appearing about the fourth day and loosening on the sixteenth to the twentieth day. This membrane was unaltered by the local application of the usual aqueous or alcoholic antiseptics, even though hydrogen peroxide had been used as a prior cleansing agent. When these factors were considered, i.e., the prolongation of healing time, localization of a slough, and the annoying discomfort and embarrassment to the patient requiring added necessity for frequent douches, the multiple sulfa cream preparation was tried. Two hundred cases were studied including 121 conizations of the cervix and 79 vaginal plastic operations.

Discussion

Within twenty-four hours after operation, or upon the removal of vaginal packs or cervical wicks, approximately 5.0 Gm. of multiple sulfa cream was

inserted into the vaginal canal twice daily. The patients were examined twice weekly following the seventh postoperative day. At the time of each office visit the patients were questioned as to the odor, number of napkins used to control leucorrheal discharge, and localized pelvic discomfort.

One of the most annoying symptoms, the malodorous discharge, was found nonexistent in all the treated cases. On speculum inspection, the operative site was red and appeared always as a clean granulating surface without a superficial membrane attached, and no apparent slough present.

It was noted in the conization series that at the tenth and eleventh days, epithelialization was in active progress as evidenced by the furred appearance at the advancing reparative edges of the vaginal portions of the coned canal. Healing was completed as early as the sixteenth postoperative day and as late as the twenty-fourth postoperative day in contrast to twenty-eight days[22] to forty-two days.[23] See Table II illustrating these time factors.

TABLE II. OPERATIVE PROCEDURES.* TWO HUNDRED CASES TREATED WITH COMPOUND SULFA CREAM IN THE POSTOPERATIVE PERIOD

	NO. OF CASES	AVERAGE TIME OF HEALING
Anterior colporrhaphy	29	16 days
Perineorrhaphy	25	17 days
Colpocleisis	2	17 days
Cervical amputation	6	22 days
Third degree tear repair	2	11 days
Vaginal hysterectomy	15	18 days
Cervical conizations	121	20 days
	200	

*Several types of lower canal surgical procedures were performed upon single cases.

In 899 conization cases Miller and Todd[23] found an incidence of proved stenosis in 6.46 per cent with a probable incidence in an additional 2.51 per cent. In our series the cervical canals were sounded upon the 21st day in all conization cases and no occlusions were discovered. There was, however, a slight increase in the amount of granulation ooze noted during the second postoperative week, as compared to the amount seen previously in patients where slough was present in those who had not beeen treated with the multiple sulfa cream in the postoperative period. Before this treatment was instituted we noted an increase in the amount of bleeding at about the twenty-fifth day, which was then attributed to the detachment of the sloughing membrane covering the thrombosed and infarcted vessels. Since the same bleeding takes place with multiple sulfa therapy during the second postoperative week, and since this stage corresponds to the twenty-fifth day or thereabouts in the healing schedule without therapy, it may be the ooze is occasioned by the beginning of the epithelialization and onset of angiomatous proliferation. Histologic work on this subject is now in progress.

In this series of cases one patient developed a parametrial abscess which necessitated posterior colpotomy. The operative vaginal site, however, showed rapid healing. Following evacuation of the parametrial abscess, complete recovery ensued.

In the sixty-four vaginal plastic cases the same rapid healing time and decrease in discharge was noted. However, where complete epithelialization occurred earlier, the sutures remained in place even after thirty days, and in many cases the twenty-day catgut had to be removed much as any nonabsorbable suture material.

In these simple vaginal plastic procedures not involving cervical surgery, there was seldom any abnormal increase in vaginal discharge noted. In this group of cases the compound sulfa cream was used solely to decrease the bacterial flora. Of particular interest were two LeForte colpocleisis operations, done on women both past 70 years of age. In both instances the healing was prompt and complete. Needless to say, meticulous care was exercised in the introduction of the multiple sulfa cream along the lateral troughs.

Summary

In an attempt to enhance healing and obtain a corollary decrease in the postoperative vaginal discharges, a newly developed multiple sulfa cream was evaluated. Its component sulfonamides included sulfathiazole, N-acetyl-sulfanilamide, N-benzoyl-sulfanilamide in addition to urea peroxide. The three sulfa compounds were found useful in combatting the secondary bacterial invaders which grow more luxuriantly at the elevated and optimally pathogenic pH levels. The urea peroxide proved useful in improving the bacteriostatic and bacteriocidal action of the sulfonamide preparation itself. Urea peroxide is also bacteriocidal and does exert some debriding action upon the denuded mucosal surfaces.

Bacteriologic and histologic studies in vivo and in vitro were carried out to insure low toxicity of such topically applied multiple sulfa derivatives incorporated in an absorptive cream base.

Two hundred surgical patients have been carefully followed over a period of eighteen months and the clinical efficacy of the preparation was demonstrated.

Conclusions

1. A recently developed compound sulfa cream, embodying normal physiologic and chemotherapeutic principles, was studied and its efficacy in treating the postoperative cervix and vagina was demonstrated in 200 gynecologic cases.

2. The high bacteriostatic and bacteriocidal action of this multiple sulfa topical preparation, at the important pH ranges of 4.6, 5.2, and 7.0 was demonstrated clinically and in the laboratory. As the reparative processes of lower genital tract mucosa increased the elevated pH of the surface infected wounds regressed to normal hydrogen ion values ranging between pH of 4.0 to 5.0.

3. The compound sulfa cream is a sound addition to the postoperative period not only because of ease of administration and the fact that annoying vaginal discharges were decreased to a minimum but primarily because the healing time of such mucosal surfaces was reduced to 50 per cent of what it was previously as compared to control cases.

The author is indebted to Dr. Camille J. Stamm for his kindness in contributing his cases to this study; and to the Ortho Research Foundation for making available full experimental laboratory data.

References

1. Rakoff, A. E.: Nat. Com. on Maternal Health, 109-132, 1943.
2. Rakoff, A. E.: Feo, L. G., and Goldstein, L.: AM. J. OBST. & GYNEC. **47**: 467-494, 1944.
3. Cruickshank, R., and Sharman, A.: J. Obst. & Gynaec. Brit. Emp. **41**: 208-226, 1934.
4. Lewis, R. M.: AM. J. OBST. & GYNEC. **26**: 593, 1933.
5. Krumm, J. F.: AM. J. OBST. & GYNEC. **31**: 1035, 1936.
6. Traut, H. F., Block, P. W., and Kuder, A.: Surg., Gynec. & Obst. **63**: 7, 1936.
7. Weinstein, L., Wawro, N. W., Worthington, R. V., and Allen, E.: Yale, J. Biol. & Med. **11**: 141, 1938.
8. Weinstein, L., Bogin, M., Howard, J. H., and Finkelstone, B. B.: AM. J. OBST. & GYNEC. **32**: 211, 1936.
9. Trussell, R. E., and MacDougal, R. F.: AM. J. OBST. & GYNEC. **39**: 77, 1940.
10. Schottmüller, H.: München. med. Wchnschr. **75**: 1480, 1928.
11. Schottmüller, H.: München. med. Wchnschr. **75**: 1634, 1928.
12. Harris, J. W., and Brown, J. H.: Bull. Johns Hopkins Hospital **44**: 1, 1929.
13. Colebrook, L., and Hare, R. J.: J. Obst. & Gynaec. Brit. Emp. **40**: 609, 1933.
14. Cowles, P. B.: Yale J. Biol. & Med. **14**: 599, 1942.
15. Lehr, D.: Proc. Soc. Exper. Biol. & Med. **58**: 11, 1945.
16. Weinstein, L., and McDonald, A.: Science **101**: 44, 1945.
17. Olson, M., Slider, E., Clark, W. G., and MacDonald, R.: Proc. Soc. Exper. Biol. & Med. **49**: 396, 1942.
18. Tsuchiya, H. M., Tenenberg, D. J., Clark, W. G., and Strakosch, E. A.: Proc. Soc. Exper. Biol. & Med. **50**: 262, 1942.
19. Tenenberg, D. J., Tsuchiya, H. M., Clark, W. G., and Strakosch, E. A.: Proc. Soc. Exper. Biol. & Med. **51**: 245, 1942.
20. Schnitker, M. A., and Lenkoff, C. D.: J. Lab. & Clin. Med. **29**: 889, 1944.
21. Carrington, G. L.: AM. J. OBST. & GYNEC. **51**: 90, 1946.
22. Crossen, H. S., and Crossen, R. J.: Operative Gynecology, St. Louis, 1943, The C. V. Mosby Co., pp. 334-341.
23. Miller, N. F., and Todd, O. E.: Surg., Obst. & Gynec. **67**: 265, 1938.
24. Cantarow, A., and Trumper, M.: Clinical Biochemistry, Philadelphia, 1945, W. B. Saunders Co., p. 29.

ANEMIAS OF PREGNANCY

PETER J. TALSO, M.D.,* AND WILLIAM J. DIECKMANN, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology of The University of Chicago and The Chicago Lying-in Hospital)

A DECREASE in the hemoglobin concentration, hematocrit, and erythrocyte count of the peripheral blood occurs during pregnancy. True anemia of pregnancy has been defined as a condition in which these constituents are reduced below the level considered physiologic for the period of gestation.[1] Various minimal hematologic standards for normal pregnancy have been proposed.[1, 2, 3] For this study a hemoglobin of 10 Gm. per cent, a hematocrit of 33 per cent, and an erythrocyte count of 3.36 million per cubic millimeter were considered as the minimal normal values between the twelfth and the thirty-sixth week of pregnancy.[2]

Many observers have described satisfactory therapeutic results using iron preparations alone or in combination with other substances.[1, 4, 5, 6, 7] Others have ascribed little efficacy to these agents.[2, 8] In view of these discrepancies we feel that adequate comparison with simultaneously observed controls is lacking. As a result, this study was undertaken to review the cases of anemia of pregnancy followed at the Chicago Lying-in Hospital during the past several years.

Initial and periodic hemoglobin determinations are very important parts of prenatal and postpartum care. The usual methods for determining hemoglobin—either with the visual or photoelectric colorimeter—require very small amounts of blood, 0.02 ml. and dilutions of 100 to 400 times. Thus the combined error of the pipette and chamber, as well as the technician may be 7 to 15 per cent. The hematocrit and erythrocyte count are methods for determining the number of red blood cells per unit of blood. The hematocrit has a closer correlation with the hemoglobin concentration than the red cell count, because the error in the former is approximately 2 per cent, while the minimum error in the red cell count is over 8 per cent. For over ten years we have been using the hematocrit determination on heparinized blood as a screening method. Any patient who is less than twelve weeks pregnant or more than six weeks post partum whose hematocrit is less than 37 volumes per cent is referred to the antepartum anemia clinic. Between twelve weeks and thirty-six weeks gestation the lower limit of the hematocrit is 30, and between thirty-six weeks and term the lower limit is 32 volumes per cent. The procedure in the anemia clinic is to obtain additional history and special examinations as to possible causes for the anemia. A diet history is obtained in some instances. The hemoglobin,

*Present address: Medical Department Field Research Laboratory, Fort Knox, Kentucky.

hematocrit, red cell count, leucocyte count, and differential determinations are made. The various indices, mean corpuscular hemoglobin, and cell volume, etc., are determined and the anemia classified. For purposes of this study, all cases complicated by blood loss, toxemia, and infection were excluded.

After a preliminary observation period of two to six weeks during which the determinations were repeated, therapy was begun. All treated cases received iron in doses accepted to be adequate.* Also, in certain of the cases accessory hematopoietic substances such as vitamins of the B complex, desiccated hog's stomach, and liver extract were administered in addition to the iron. In the graphs and tables these are included under the heading: Iron and Vitamins. After the institution of therapy the cases were followed at biweekly intervals until three to six months post partum with periodic blood studies. Patients with hemoglobin concentrations of six grams per cent or less were hospitalized for a more detailed study. In some cases transfusions of whole blood served as the principal therapy given or as a supplement to other treatment.

Results

Two hundred fifty cases were studied. These have been classified as to mean corpuscular volume[9] and therapy administered (Table I). The mean corpuscular hemoglobin concentration[9] was determined in each case, and it was found that 42 per cent were normochromic, 56 per cent hypochromic, and 2 per cent hyperchromic. At the time of their first visit 57 per cent of the entire group were anemic. This represented 61 per cent of the treated group and 48 per cent of the controls.

TABLE I

		GAIN OF Hb IN GM. IN 21 DAYS				
		A	B	C	D	E
	NO. OF CASES	DECREASED OR UNCHANGED	0 TO 1.5 GM.	1.6 TO 3.3 GM.	OVER 3.3 GM.	MEAN GAIN GM.
Macrocytic						
Controls	12	5	5	1	1	0.82 ± .20*
Iron alone	31	10	15	6	0	0.73 ± .09
Iron and vitamins	19	6	8	4	1	0.92 ± .15
Transfused	2					
Subtotal	64					
Microcytic						
Controls	39	8	23	5	3	0.86 ± .09
Iron alone	53	11	24	17	1	1.24 ± .09
Iron and vitamins	32	9	13	8	2	1.04 ± .14
Transfused	9					
Subtotal	133					
Normocytic						
Controls	25	13	11	1	0	0.24 ± 0.6
Iron alone	27	10	12	5	0	0.73 ± .12
Transfused	1					
Subtotal	53					
Total	250					

*Probable error of mean.

*Iron was prescribed in the following daily doses: Ferrous sulfate, 1.0 Gm.; Ferric ammonium citrate, 5.0 Gm.; or Ferrous Carbonate, 5.0 Gm.

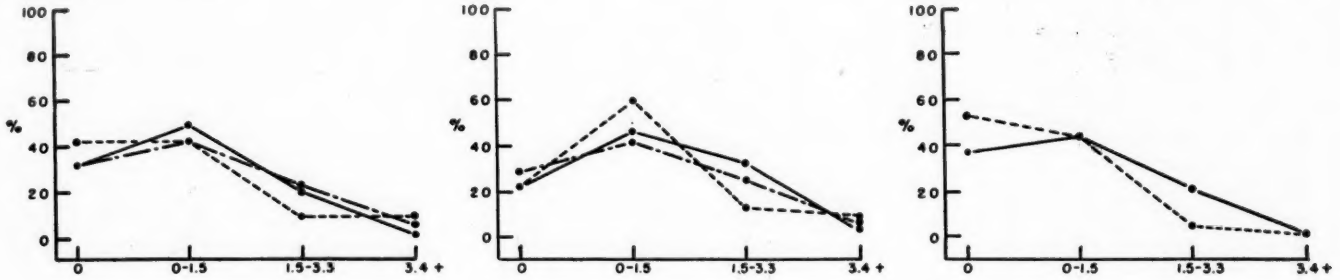


Fig. 1.

TABLE II

COMPARISON OF TREATED GROUP WITH CONTROLS AT BEGINNING OF OBSERVATION PERIOD				
	MEAN AGE	MEAN NO. OF PREG.	MEAN Hb	MEAN WEEK OF PREGNANCY
Untreated controls	28.3 ± .5	3.2 ± .2	9.1 ± .09	31.4 ± .4
Treated group	27.5 ± .3	3.2 ± .1	9.0 ± .06	31.2 ± .3

TABLE III

	MACROCYTIC		MICROCYTIC		NORMOCYTIC	
	Hb	SD*	Hb	SD*	Hb	SD*
Controls	10.2	0.7	9.6	1.4	9.8	1.3
Treated group	11.1	1.4	10.6	1.9	11.3	1.7

*SD. Standard deviation.

During adequate therapy the expected rate of hemoglobin formation is 0.078 Gm. per day, and the maximum is reached between the second and fourth week.[10, 11] For this reason a twenty-one-day observation period was selected in order to evaluate the effects of treatment. At the beginning of this period the treated group showed no significant differences from the controls (Table II).

The gain in hemoglobin concentration in the various groups during the three weeks of observation is recorded in Table I (Columns A to D). Inspection of these data reveals that the number of cases showing the expected gain in hemoglobin during this observation period, 1.6 Gm. in twenty-one days, is only slightly greater in the treated groups than in the controls. Fig. 1 presents these data in graphic form, the gain in grams of hemoglobin being plotted along the abscissa, and the percentage of cases along the ordinate. When the mean values in the separate groups are compared, the difference between the controls and the treated cases is not statistically significant (Table 1, Column E).

Comparison of the hemoglobin values of the treated groups and the controls at term failed to reveal any significant differences between the two (Table III). Further, while 51 per cent of the controls were anemic at term, 27 per cent of the treated group were still anemic at that time.

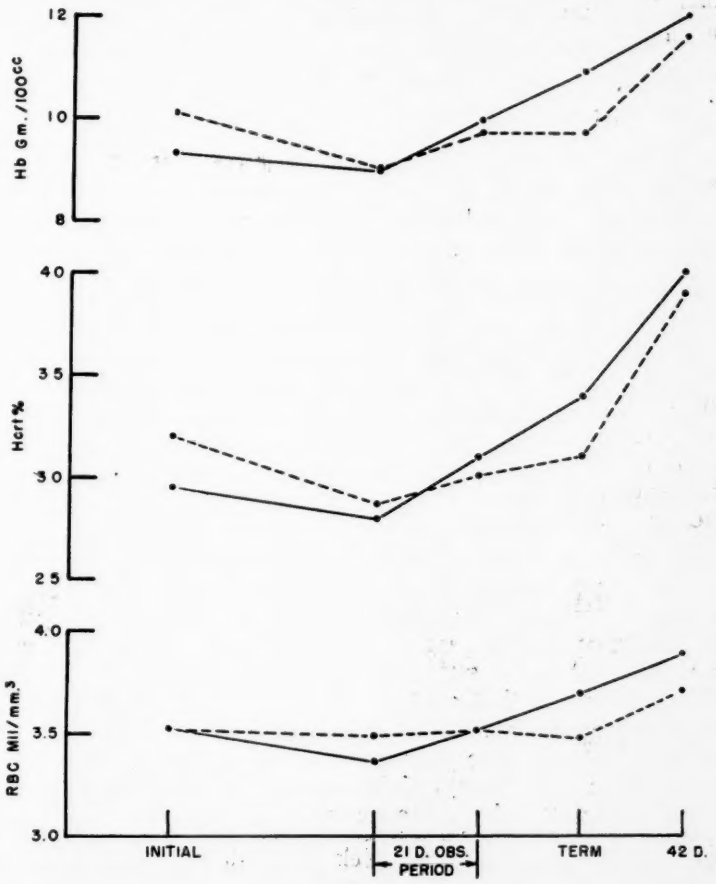


Fig. 2.

Many patients did not return for postpartum examinations, and therefore data were not uniformly available for comparison. The hematologic values of both groups, however, showed a rapid return to normal levels during this period (Fig. 2).

Diet histories of forty-two patients were analyzed by our nutritionist. Using the National Research committee's criteria for iron, and Burke's criteria for protein, she classified the diets as follows: poor iron and poor protein intake—14 per cent; poor iron, fair protein—31 per cent; poor iron and good protein—17 per cent. Thus 62 per cent had a low intake of iron. However, these diets may not be as deficient as they seem to be because they were based on patients' estimates, and we have learned that they are inaccurate and that the food must be weighed and recorded immediately. We are now doing this.

In certain cases transfusions of whole blood served as the principal therapeutic agent as indicated above. In these, transfusions were given as emergency measures because of rapidly falling hemoglobin values. Also, in five of the controls and in eleven of the treated cases, transfusions were administered after the completion of the twenty-one-day observation period when the patient had reached term before the hemoglobin had returned to normal levels. No hematologic data on the transfused cases are included here, as blood was uniformly given in quantities adequate to bring the hemoglobin to normal levels.

Discussion

The plasma volume during pregnancy increases 25 per cent and the red cell volume only 23 per cent, thus accounting for the physiologic anemia of pregnancy.[12] Reported bone marrow studies have revealed a normal erythroid pattern, and served to confirm the concept that this condition arises from hydration alone.

The cases in the present study represent those in which the hematologic findings fell below the minimal physiologic values. Changes in the peripheral blood may reflect both pathologic and physiologic processes simultaneously and their detection is characterized by certain inherent errors.[2] As a result of these factors the effects of any therapeutic agent must be evaluated cautiously.

Classically, microcytic hypochromic anemias are associated with iron deficiency. During pregnancy an inadequate diet, defective absorption from the gastrointestinal tract, and increasing fetal demands have been accused of precipitating this condition. Wolff and Limarzi[13, 14] report a normoblastic hyperplasia of the bone marrow in such cases. These workers and others[1, 5, 6] conclude that these anemias are the result of an iron deficiency and can be corrected by administering simple iron salts. Some workers stress the importance of diet in their prevention and correction.[1, 15, 17] Others indicate that although an adequate diet is important from the standpoint of maternal health, the quality of the diet has little effect on the hematologic findings except in the extremes.[3, 8, 16] Changes in the gastrointestinal secretory function occur in most pregnant women,[17] yet no significant correlation exists between the decreased gastric acidity and the incidence of anemia.[3] Further, studies with radioactive materials during pregnancy have revealed that iron is absorbed at two to ten times the normal rate.[18] The amount of iron necessary for fetal growth is negligible during the first twenty-eight weeks and yet it is during this period that there is the greatest fall in the maternal hemoglobin concentration. It is only during the last twelve weeks, when the fetal weight increases from approximately 1,000 Gm. at twenty-eight weeks to 3,400 Gm. at term, that the iron requirement of the fetus becomes appreciable. But even at term, when the actual amount of iron required by the fetus is greater, the total fetal content is only 280 mg., which could be furnished by the iron from 600 c.c. of maternal

blood. Furthermore, it is during this last twelve weeks that the maternal hemoglobin concentration is either stationary or is increased. Thus, during the maximum fetal requirement, the hemoglobin concentration also increases.[2, 8]

The results of the present study indicate that during pregnancy the rate of hemoglobin formation is not significantly altered by the administration of iron alone or in combination with accessory substances. In the light of the foregoing material this suggests that these anemias are not due to a simple iron deficiency, but that some other factor is lacking or that the defect lies in the mechanism of postabsorptive iron utilization.

The "pernicious-like" or megaloblastic anemia of pregnancy occurs only rarely.[19] Several workers suggest that the diagnosis can only be made from studies of the bone marrow and that the peripheral blood findings are often misleading.[13, 14, 20] It is unlikely that the macrocytic anemias in the present series are examples of the megaloblastic type of anemia.

Summary

Two hundred fifty cases of anemia in pregnancy were studied to evaluate the effects of treatment with iron alone and in combination with accessory factors. Controlled observations indicate that the administration of these substances does not increase the rate of hemoglobin formation significantly.

References

1. Bethell, F. H., Gardiner, S. H., and MacKinnon, F.: Ann. Int. Med. **13**: 91, 1939.
2. Adair, F. L., Dieckmann, W. J., and Grant, K.: AM. J. OBST. & GYNEC. **32**: 560, 1936.
3. Watson, H. G.: AM. J. OBST. & GYNEC. **35**: 106, 1938.
4. Labate, J. S.: AM. J. OBST. & GYNEC. **38**: 48, 1939.
5. Tolland, O. J.: AM. J. OBST. & GYNEC. **31**: 640, 1936.
6. Strauss, M. B.: J. A. M. A. **102**: 281, 1934.
7. Strauss, M. B., and Castle, W. B.: Am. J. M. Sc. **185**: 539, 1933.
8. Dieckmann, W. J., and others: AM. J. OBST. & GYNEC. **47**: 357, 1944.
9. Wintrobe, M. M.: Clinical Hematology, Philadelphia, 1942, Lea & Febiger, pp. 72, 78.
10. Murphy, W. P.: Arch. Int. Med. **51**: 656, 1933.
11. Fullerton, H. W.: Edinburgh M. J. **41**: 99, 1934.
12. Dieckmann, W. J., and Wegner, C. R.: Arch. Int. Med. **53**: 71, 1934.
13. Wolff, J. R., and Limarzi, L. R.: J. A. M. A. **128**: 482, 1946.
14. Wolff, Jr. R., and Limarzi, L. R.: AM. J. OBST. & GYNEC. **51**: 447, 1946.
15. Strauss, M. B., and Castle, W. B.: Am. J. M. Sc. **184**: 663, 1932.
16. Fullerton, H. W.: Brit. M. J. **2**: 577, 1936.
17. Strauss, M. B., and Castle, W. G.: Am. J. M. Sc. **184**: 655, 1932.
18. Balfour, W. M., and others: J. Exper. Med. **76**: 15, 1942.
19. Davidson, L. S. P., Davis, L. J., and Innes, J.: Brit. M. J. **2**: 31, 1942.
20. Callender, S. T. E.: Quart. J. Med. 13, Nos. 50-51: 75, 1944.

ANTENATAL BLOOD GROUP DETERMINATION*

A Preliminary Report

S. H. POLAYES, M.D., SAMUEL LUBIN, M.D., AND JAMES MCNALLY JR.
BROOKLYN, N. Y.

(From the Department of Pathology, Prospect Heights Hospital, and the Department of Pathology and Obstetrics and Gynecology, Cumberland Hospital)

IN THE course of a previous study[1] on isoimmunization with the A and B agglutinogens, it became apparent that a high anti-A or anti-B agglutinin titer in the serum of a pregnant woman is an indication of isoimmunization of the mother against the corresponding antigen in the fetus. In the case of a primipara, the immunization was naturally ascribed to the fetus of the existing gestation, while in the case of a multipara, either the existing gestation or any of the previous pregnancies could have acted as the immunizing agent.

In order to obtain more data on this hypothesis, a series of 100 pregnant women with blood groups O, A or B were chosen for study. Among them were 19 cases of heterospecific pregnancy. In each of the 100 cases, the anti-A and anti-B agglutinin titer of the serum was determined. As a control series, the bloods of 50 nulligravidas (O-A-B) who were never subjected to immunization by pregnancy or injection of blood were similarly titrated. In the pregnant women with children of blood groups compatible with their own, the average anti-A or anti-B titer of their serum did not exceed 1:500, and in no instance was the titer found to be above 1:1,280. In the series of nulliparas, about 95 per cent of the cases showed a titer ranging from 1:10 to 1:300. In no instance did the titer exceed 1:1,280. In neither of the latter two groups was there a single instance in which the anti-A or anti-B agglutinin titer reached a level of 1:2,000. In contrast to these values, the women with heterospecific pregnancy showed a much higher titer. In the majority of these instances it ranged from 1:500 to 1:5,000, and some reached values as high as 1:20,000 or more.[2] Titers of 1:2,000 or over were considered significant, since, as stated above, none of the nulliparas nor multiparas with babies of compatible blood groups showed such high values. Therefore, this titer was arbitrarily chosen as a base line above which any agglutinin titer would indicate isoimmunization against its specific antigen A or B. Thus, a woman of group B, whose serum showed an anti-A agglutinin titer of 1:2,500, was presumed either to be bearing (particularly of a primigravida), or to have previously borne a group A offspring. This presumption was confirmed in each case in which the agglutinin titer exceeded 1:2,000, as seen from Table I.

Comments

A study of Table I suggests that it may be possible to foretell the baby's blood group from a study of the titer of the group specific agglutinins in the serum of the mother. In several instances (not included in this table) in which the mother's serum showed an agglutinin titer approximating 1:2,000, but in which the mother was delivered of a group O baby, examination of her pre-

*Aided by a grant from the United Hospital Fund of New York City.

TABLE I. ANTENATAL BLOOD GROUP DETERMINATION BY ANTIBODY TITRATION OF MOTHER'S SERUM (ANTI-A AND ANTI-B AGGLUTININ TITERS EXCEEDING 1:2,000)

CASE NO.	NUMBER OF PREGNANCIES	MOTHER'S GROUP	TITER	CHILD'S GROUP
35	1	0	Anti-B 2560	B
38	9	0	Anti-B 20,480	B
39	1	0	Anti-A 5120	A
42	0	0	Anti-A 2560	A
43	2	B	Anti-A 2560	AB
44	1	0	Anti-A 5120	A
76	1	A	Anti-B 2560	AB
86	1	0	(Anti-A 5120) (Anti-A Milk 5120)	A
88	1	0	Anti-A 20,000	A
103	2	0	Anti-A 5240	A
110	3	0	Anti-A 5120	A

vious offsprings showed them to belong to group A, B, or AB, as the case may have been. While a titer lower than 1:2,000 in a group O mother did not exclude the possibility of a group A or B offspring, the reverse was not true. No instance was found in which a mother with an agglutinin titer of 1:2,000 or over did not have an offspring with the corresponding specific antigen. Admittedly, the present series is not a very large one, but the nonstatistical evidence thus far may be considered quite striking. A case in point is case 43. The mother here is a group B, and therefore normally should have anti-A agglutinin in her serum. But the fact that the titer of the agglutinin was found to be as high as 1:2,500 led to the presumption that the offspring in utero must possess the A antigen, since, as far as could be determined, the mother had not been exposed to immunization with the A antigen previously. As is seen from Table I, this was a correct presumption, since blood grouping tests after birth proved the child to be a group AB. That this reasoning is equally applicable to instances of anti-B agglutinin, is borne out in case 76, where the anti-B agglutinin in a group A mother was found to be 1:2,560. The prediction that the yet unborn offspring contained the B antigen was confirmed, the child having been found to be a group AB at birth. Incidentally this baby was a girl, one of a twin, the other being a boy and a group A.

The highest titer in the tabulated cases was 1:20,000 or slightly above. This value was found in one case of a primipara and in another of a multipara (a para ix), showing that the titer of the antibody does not depend upon the number of pregnancies.

Case 86 showed an anti-A agglutinin titer of 1:5,120 in the milk as well as in the serum; hence (as in the case of Rh isoimmunization) the contraindication for breast feeding these infants.

The preponderance of group O mothers in the above table is probably a hapchance in this particular group of selected heterospecific pregnancies. Group AB, of necessity, had to be excluded from this series, since there are no anti-A or anti-B agglutinins in their serum.

The titers given are those obtained by the agglutination (saline dilution) technique. With the so-called conglutination technique (using homologous or AB serum as a diluent) much higher values were obtained in most, although not all of the cases. In fact, in a number of instances the "conglutinin" titer was considerably lower than the agglutinin titer.

Conclusions

1. In heterospecific pregnancies the anti-A and anti-B agglutinin titer in the mother's serum may rise to much higher levels than those found in nulliparas, or in mothers with offsprings of compatible blood groups.

2. When the anti-A or anti-B agglutinin titer in a primigravida's serum rises to a level of 1:2,000 or over, it may be presumed that the fetus in utero possesses in its blood the corresponding antigen A or B. In the case of a multipara, the immunizing A or B antigen will be found to be present in at least one of her previous children or in the offspring of the present pregnancy.

3. In primiparas and in certain multiparas with heterospecific pregnancy, the baby's blood group sometimes may be determined antenatally by the titration of the group specific antibodies in the mother's serum.

References

1. Polayes, S. H.: Am. J. Dis. Child. 69: 99, 1945.
2. Polayes, S. H., and McNally, J., Jr.: Am. J. Clin. Path. (in press).

MESODERMAL MIXED TUMOR OF THE VAGINA: REPORT OF CASE

GEORGE H. MURPHY, M.D., AND JAMES W. DUSHANE, M.D., ROCHESTER, MINN.

(From the Department of Pathology, Mayo Foundation, and the Section on Pediatrics, Mayo Clinic)

THE following case, while primarily a pathologic problem, presents features of interest to the clinician as well. This report is of the third mesodermal mixed tumor diagnosed at the Mayo Clinic, two cases of such a tumor of the uterus having been reported by McDonald, Broders and Counseller; the tumor in the case reported herein is the first such tumor of the vagina found here.

Report of Case

A white child, 33 months of age, was admitted to the clinic on Nov. 6, 1946. Obstetric and family histories were irrelevant. About November, 1945, the parents had noticed the child scratching the vulva and saw a little blood. Examination by their local physician in February, 1946, had revealed a small tumor presenting at the vulva. The tumor was excised in March, 1946; the histologic diagnosis was "botryoid sarcoma (rhabdomyoma) of the vagina." The operative site received radium therapy seven months prior to her admission to the clinic, and the radium therapy was followed by roentgen therapy over a period of about two months. The child was apparently well for another two months but then more vaginal bleeding was noted and she was given further roentgen therapy. On admission to the clinic she presented no actual signs of distress, but the parents said she held back urine as long as possible. A satisfactory examination was not possible as the child was too apprehensive, but a soft mass was palpated in the vagina.

At operation on Nov. 8, 1946, a soft, polypoid tumor mass was found completely filling the vagina. The mass was removed, for the most part, and was found to originate on the right anterior wall of the vagina over an area of 5 by 2 centimeters. Because of the malignant nature of the tumor, as confirmed at operation by examination of a fresh frozen section, and its infiltration of at least the vaginal wall, the surgeon did not feel that a sufficiently radical operation could be attempted. The patient was discharged a few days later in good condition, but the parents were told that the prognosis was extremely grave.

Pathologic Findings.—The tumor, in pieces, weighed 24 Gm., forming an aggregate mass about 2.5 by 6 by 4 centimeters. It had the appearance of a group of polyps each about 2 cm. in diameter, the classical so-called botryoid morphology. The surface was smooth and gray-white except for a few hemorrhagic areas. The tumor was of firm consistency and could be cut easily; the cut surface was homogeneous and glistening.

Representative portions of the tumor were fixed in 10 per cent solution of formalin (3.8 per cent solution of formaldehyde), absolute alcohol, and Zenker's solution. Paraffin sections were stained by hematoxylin and eosin, Masson trichrome, Bodian and elastin H methods; sections also were stained for mucin by a modified Mayer mucicarmine[4] method and for glycogen by the Best carmine method.

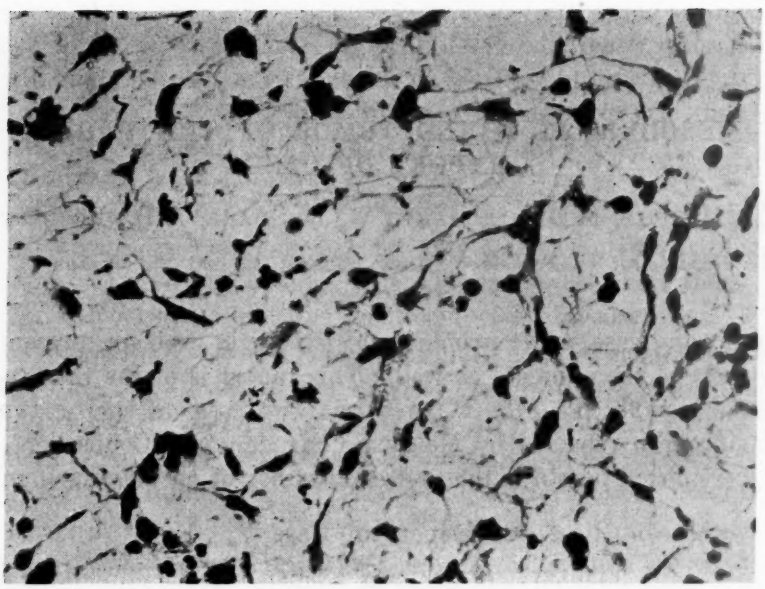


Fig. 1.—Myxomatous connective tissue network (Bodian ×335).

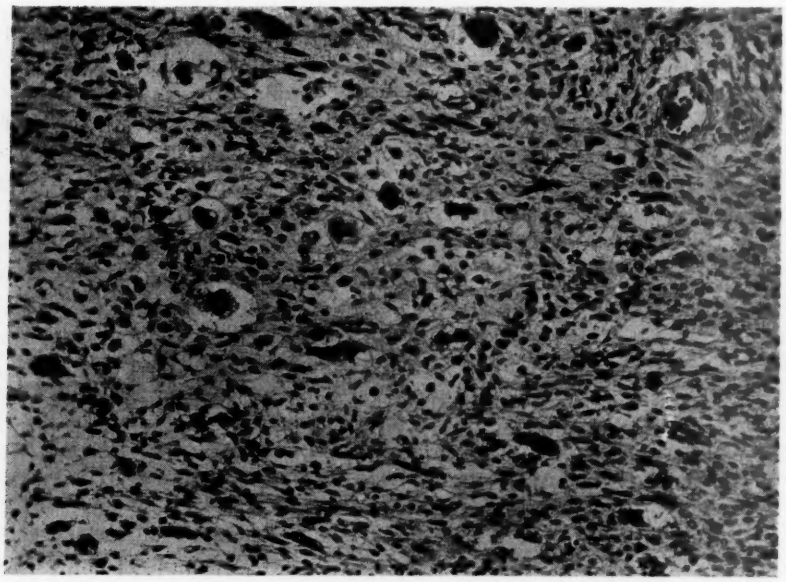


Fig. 2.—Plump spindle cell stroma with giant cells (hematoxylin and eosin ×100).

Histologically the greater part of the tumor consisted of myxomatous connective tissue: spindle and star-shaped cells connected by delicate strands to form a network (Fig. 1). In other more cellular areas plump spindle cells with prominent nuclei and nucleoli and with mitotic figures were seen; interspersed were multinucleated tumor giant cells with large, often deeply staining nuclei and scanty cytoplasm (Fig. 2). Still other cellular areas showed rather irregular, round, or elongated cells, many with longitudinal striations and some with well-defined cross striations (Fig. 3): young striated muscle cells; scattered among these were embryonic myoblasts, large, often multinucleated cells

Fig. 3.—Young striated muscle fiber (Bodian ×1,000).

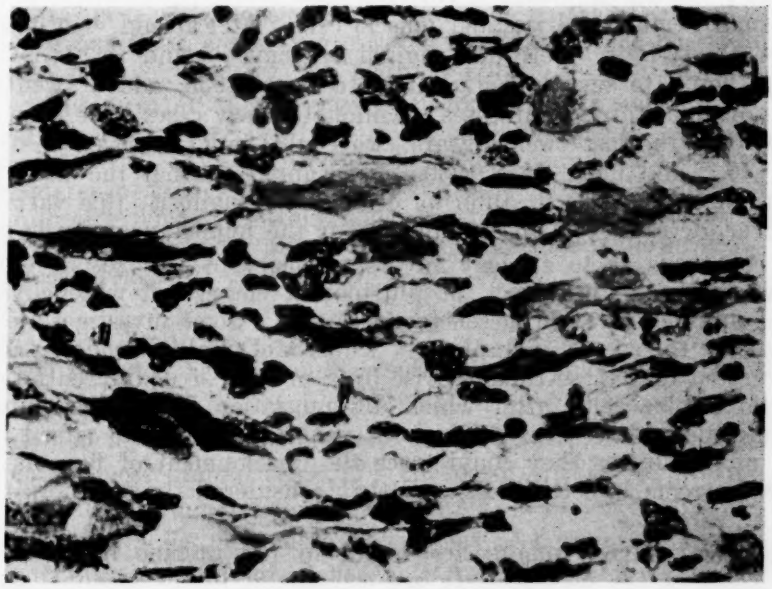


Fig. 4.—Myoblasts with myxomatous tissue matrix (Bodian ×430).

with a relatively large amount of granular cytoplasm (Fig. 4). Some areas showed a considerable amount of collagen, but no cartilage or bone was found in the sections examined. Adult type squamous epithelium covered the surface of the tumor. Staining for mucin gave positive results in the myxomatous appearing areas and some extracellular and intracellular glycogen was noted. A few blocks showed gross degeneration with hemorrhage, and infiltration with acute and chronic inflammatory cells, doubtless a consequence of the radiation therapy.

Mesodermal mixed tumors form an ill-defined group of malignant neoplasms of the uterus, cervix, and vagina. By definition they are monodermic in origin, as opposed to the origin of teratomas which is tridermic, they develop from mesoderm and they consist of heterotopic and highly malignant tissues.

The literature contains confusing reports as to the nature and incidence of these tumors. McFarland,[12] in an extensive review of the subject, listed 116 different names from the literature for mesodermal type tumors of the genital tract; among the best known was the term "botryoid sarcoma" after the "traubiges Sarkom" of Pfannenstiel (1892). McFarland suggested the name "dysontogenetic tumors" for the whole group. The bulk of his data is not in the literature, but Amolsch would seem to have reviewed it when he reported 447 cases of mesodermal mixed tumors of the uterus, cervix and vagina, so diagnosed on the basis of the presence of embryonic myxomatous tissue. He and subsequent writers followed the terminology of Kehrer and called them all "mesodermal mixed tumors." Lebowich and Ehrlich[9] and Ehrlich[5] limited the group sharply by demanding the finding of embryonal striated myoblasts in accordance with the criteria set forth by Läwen; they could find reports of but fourteen such tumors of the body of the uterus in the literature. Glass and Goldsmith were not quite so exacting in their requirements and found records of ninety-four mesodermal mixed tumors of the uterine body and cervix. The incidence of the vaginal group is even more uncertain. Kehrer listed reports of nine vaginal sarcomas of children that showed heterotopic mesodermal tissues, usually embryonal striated muscle cells. McFarland,[11] in 1911, found reports of thirty-four "botryoid vaginal sarcomas," and by 1935[12] he had raised this figure to seventy-four. Bergström, in 1936, added twenty to McFarland's original thirty-four cases. Undoubted new cases have been reported infrequently in the last twenty-years; we could find but seven in the literature,[1, 2, 12, 18, 19] and none since 1939. It is apparent that the wide variation in all these figures is due to differing criteria of diagnosis; this variation does not, however, detract from the interest in, or the importance of, the group.

The consensus as to etiology favors a theory of cell rests[20] that is, the persistence in the genital tract, of pluripotent embryonal mesenchymal cells, capable of producing varied mesenchymal tissues. Some investigators,[15, 17] however, favor a theory of metaplasia. Thus McDonald, Broders, and Counseller suggested that these tumors arise by a process of dedifferentiation of the endometrial stroma cells, after which differentiation takes place into various types of mesodermal structures. In both of their mesodermal mixed tumors of the body of the uterus they could trace the development of fibroblasts of the endometrial stroma into cartilage, and they considered these tumors to be true endometrial sarcomas.

Mesodermal mixed tumors are found in the uterine body, cervix, and vagina. Those of the uterine body are commonest in the menopausal or postmenopausal age groups, those of the cervix are commonest in the reproductive period, while those of the vagina have all occurred in very young patients, mostly those less than three years of age.

Because of the varying criteria of diagnosis, it is difficult to assess the relative incidence in the various sites. Glass and Goldsmith gave the ratio of those in the body of the uterus to those in the cervix as 1.6:1, while Lebowich and Ehrlich, with their stricter criteria, gave a ratio of 1:3. Shaw found those of the body of the uterus slightly less common than those of the cervix, a ratio of about 1:1.5. As has been indicated, the number of vaginal tumors is uncertain, but they would seem to be the most common of the three.

Clinically, there is little that is extraordinary about mesodermal mixed tumors. The signs and symptoms closely resemble the rather vague ones associated with adenocarcinoma of the genital tract of women, vaginal bleeding and discharge being the commonest signs. Such tumors of the vagina may first be noticed when they present at the vulva.

Grossly, mesodermal mixed tumors of the uterus appear often as single or multiple polyps, while the cervical and vaginal tumors may resemble a bunch of fused polyps, the grape-cluster effect that led earlier observers to name them "botryoid sarcomas." It should be noted that a single polypoid mesodermal mixed tumor may be indistinguishable grossly from a benign polyp of the genital tract.

The microscopic picture varies greatly with the individual tumor, and there is no constant difference between those of the uterus, cervix and vagina, except that neither bone nor cartilage has been found in those of the vagina.[16, 18] They are true mixed tumors and contain numerous elements of mesodermal origin. All observers have agreed on the presence of myxomatous tissue, though not all have agreed on its nature; probably, however, it is embryonal mesenchymal tissue.[20] In addition there may be cartilage, striated and smooth muscle, myoblasts, bone, and so forth. Glandular structures, even adenocarcinoma, have been reported as occurring in the uterine tumors,[5, 8, 9, 13, 15] but these were probably incidental inclusions of benign or malignant endometrial glands.[13, 18] The histologic diagnosis of mesodermal mixed tumor may be difficult and many sections may be necessary to demonstrate heterotopic mesodermal tissue. As has been indicated, definite diagnostic criteria have not been universally accepted, but we agree with Morehead and Bowman[14] in the belief that it is unwise to exclude all but those containing striated myoblasts since mesodermal mixed tumors are a pathologic entity and a group clinically

The prognosis in all three types is uniformly bad, regardless of therapy. The over-all mortality rate has been given as 95 per cent[1]; only one five-year and one ten-year cure have been recorded.[6] The tumors have a marked tendency to local recurrence and extension after even the most radical operation, and death from local extension or from general metastasis may be expected to occur in six to twelve months.[1, 6, 9] Metastasis to distant sites is, however, a relatively infrequent occurrence.[1, 16]

Comment

The case reported herein would seem to be a typical example of a mesodermal mixed tumor of the vagina. Besides a myxosarcomatous stroma, the tumor contained myoblasts and striated muscle fibers, thus qualifying for the diagnosis in its most limited sense.[8, 9] The occurrence of a positive result in staining for mucin which refutes Pfannenstiel's contention that the so-called myxomatous tissue is actually mere edema, has been reported also by previous observers.[9, 15] The presence of glycogen is further evidence of the embryonic nature of the tumor tissue.

This case has been presented because of the rarity of the condition and to bring the entity to the attention of clinicians and pathologists alike. On gross, and even on microscopic examination, such a tumor, seen at an early stage, might easily be dismissed as a degenerating simple polyp, only to have the patient return with an infiltrating neoplasm obviously of high-grade malignancy. This has been a frequent occurrence in the recorded cases and may explain, in part, the extremely high mortality rate.

In the present case the diagnosis was made early, but in spite of local excision and radiation therapy the tumor advanced rapidly. In the light of reports in the literature and in view of the very malignant nature of these tumors, it would seem extremely doubtful that even radical operation, performed when the diagnosis was first made, would have altered, in any way, the course of the disease.

References

1. Amolsch, A. L.: Am. J. Cancer **37**: 435, 1939.
2. Moraes Barros, N., and Medina, José: Arq. de cir. clin. e exper. **1**: 46, 1937.
3. Bergström, Erik: Acta obst. et gynec. Scandinav. **15**: 491, 1936.
4. Dresbach, Mary: Personal communication to the authors.
5. Ehrlich, H. E.: Am. J. Obst. & Gynec. **43**: 1021, 1942.
6. Glass, Morris, and Goldsmith, J. W., Jr.: Am. J. Obst. & Gynec. **41**: 309, 1941.
7. Kehrer, E.: Monatschr. f. Geburtsh. u. Gynäk. **23**: 646, 1906.
8. Läwen, A.: Beitr. z. path. Anat. u. z. allg. Path. **38**: 177, 1905.
9. Lebowich, R. J., and Ehrlich, H. E.: Surgery **10**: 411, 1941.
10. McDonald, J. R., Broders, A. C., and Counseller, V. S.: Surg., Gynec. & Obst. **70**: 223. 1940.
11. McFarland, Joseph: Am. J. M. Sc. **141**: 570, 1911.
12. McFarland, Joseph: Surg., Gynec. & Obst. **61**: 42, 1935.
13. Meikle, G. J.: J. Obst. & Gynaec. Brit. Emp. **43**: 821, 1936.
14. Morehead, R. P., and Bowman, M. C.: Am. J. Path. **21**: 53, 1945.
15. Nicholson, G. W.: Guy's Hosp. Rep. **69**: 173, 1918.
16. Perlstein, Isidor: Surg., Gynec. & Obst. **28**: 43, 1919.
17. Pfannenstiel, J.: Virchows Arch. f. path. Anat. **127**: 305, 1892.
18. Shaw, Wilfred: J. Obst. & Gynaec. Brit. Emp. **35**: 498, 1928.
19. Tavernier, and Pouzet, F.: Bull. Soc. franç. de dermat. et syph. **39**: 833, 1932.
20. Wilms: Quoted by Perlstein.

LATE RECURRENCE OF CERVICAL CARCINOMA FOLLOWING RADIATION THERAPY

HAROLD SPEERT, M.D., NEW YORK, N. Y.
(From the Gynecological Service of the Roosevelt Hospital)

MORE than one-half of the patients with carcinoma of the cervix who have been unsuccessfully treated by irradiation at the Roosevelt Hospital showed a recurrence of their tumor within a year following treatment. Tumor recurrence after five years is distinctly unusual. This fact has served as the justification for the reporting of cervical cancer statistics in terms of five-year cures. Most gynecologists consider patients completely cured who survive this period with no clinical evidence of the disease.

Cervical cancer does not always run so rapid a course, however. New concepts of the pathology and biology of the early stages of the disease have been developed during recent years. Lesions which formerly were considered benign or of questionable malignancy have been associated with genuine cancer sufficiently often, either by the observation of the untreated patient during the ensuing years after biopsy, or by more intensive examination of the original specimen to merit the diagnosis of cancer themselves.

Smith and Pemberton (1934) reported one case in which six years elapsed between the original biopsy, which later was diagnosed pathologically as carcinoma, and the development of the lesion to the readily recognizable clinical entity; and in another they reported an incubation period of possibly twelve years. In a case reported by Stevenson and Scipiades (1938) clinical cancer of the cervix did not appear until eight and one-half years after the microscopic diagnosis of noninvasive carcinoma. More recently Taylor and Guyer (1946) have described another case in which seven years elapsed between a positive biopsy and the ultimate diagnosis of clinical carcinoma. It has been shown by Te Linde and Galvin (1944) that lesions diagnosed as intraepithelial carcinoma, noninvasive carcinoma, or carcinoma in situ, previously believed by some pathologists to be only precancerous, usually are found to contain regions of invasiveness if the specimen is sectioned serially. These observations strongly indicate that cancer of the cervix may develop quite slowly in its very early stages.

The purpose of this communication is to record two extraordinary cases which show that cervical carcinoma may progress slowly, or perhaps even lie dormant for long periods after treatment by irradiation, during its later clinical stages.

CASE 1.—A. G. (R. H. No. 394167) was a 52-year-old white nulliparous divorcee with a history of four spontaneous abortions. She was treated for primary carcinoma of the cervix in April, 1922, at the age of 35 years, at the Memorial Hospital. Her cervix at that time, according to a report from

Memorial Hospital, was about 5 cm. in diameter with a hard, nodular surface that was beginning to ulcerate in places. The uterus was moderately movable, but there seemed to be some "shortening of the right parametrium." Biopsy report by the late Dr. James Ewing stated "epithelioma, type uncertain" (Fig. 1). Treatment consisted of 100 mc. hours of radon administered in each of three positions by vaginal bomb on April 17, 1922, and 3,000 mc. hours administered by platinum cervix tandem on the following day. This was followed by a cycle of low voltage pelvic x-ray to two anterior and two posterior fields on April 19 and 20. The patient remained under the observation of the gynecologic department of the Memorial Hospital for twelve and one-half years, until Nov. 21, 1934. There was no evidence of residual or recurrent tumor during this period.

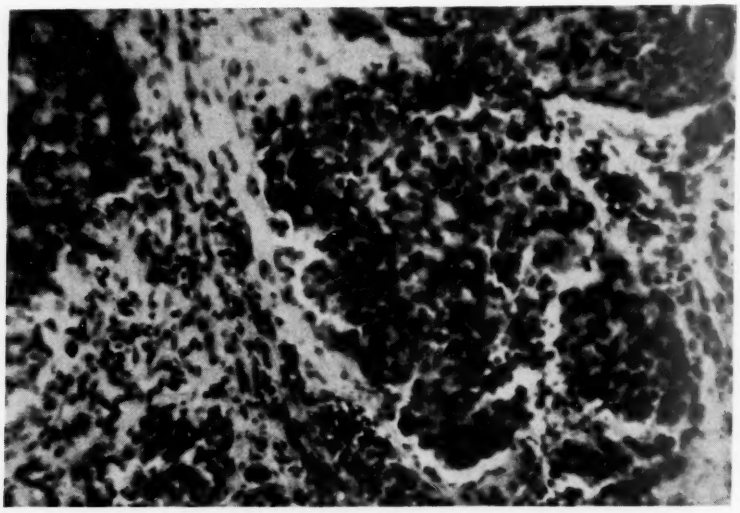


Fig. 1.—Case 1. Cervical biopsy specimen, showing anaplastic epidermoid carcinoma.

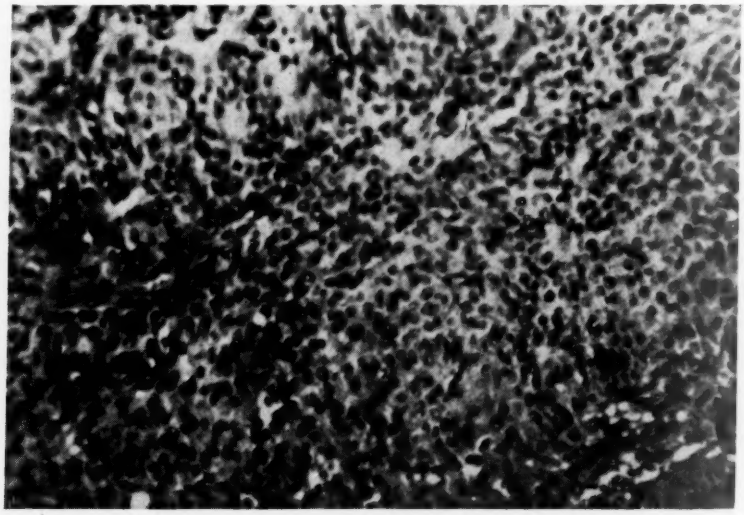


Fig. 2.—Case 1. Cervical tumor removed at autopsy seventeen and one-half years later, showing same cell type as original biopsy.

She was admitted to the Roosevelt Hospital Sept. 21, 1939, complaining of vomiting, diarrhea, and lower abdominal pain of eighteen days' duration. A hard, irregular, movable mass, about 15 cm. in diameter, occupied the right lower quadrant of the abdomen. The vagina was constricted and filled with hard friable tumor. Biopsy of this tumor showed only granulation tissue. The patient's serologic tests for syphilis were positive. Her blood urea nitrogen was 85 mg. per 100 c.c. the day after admission and rose in three days to 115. Intravenous pyelograms showed no excretion of the dye from either kidney. The patient developed a toxic erythema and died Oct. 18, 1939.

At autopsy the anatomic diagnosis was "carcinoma, primary in cervix, with extension to fundus, bladder, rectum, ovaries, Fallopian tubes, and metastatic invasion of periaortic lymph nodes, liver, and diaphragm; ureteral obstruction, bilateral, with hydroureter and hydronephrosis." The pelvic organs were greatly distorted by infiltration of the tumor. The outline of the cervix was destroyed by ulceration and necrosis, the process extending into the vaginal walls. More than three-fourth of the uterus was involved in the tumor mass. The endometrium was thin and smooth except for a single small polyp. Microscopically the tumor showed irregular masses of undifferentiated oval cells supported by small amounts of stroma, with almost complete lack of organization. The nuclei were hyperchromatic and mitoses were fairly numerous (Fig. 2). Dr. Walter Brandes, Pathologist to the Roosevelt Hospital, and Dr. Ewing compared sections of this tumor with that of the original cervical biopsy of seventeen and one-half years previously and agreed that they could not distinguish the one from the other, so completely similar were they in histologic detail.

Case 2.—N. M. (R. H. No. 13502 and No. 28803), a 33-year-old married Jamaican Negro woman with two children, was admitted to the Roosevelt Hospital for the first time on April 1, 1925, complaining of dysmenorrhea and intermittent backache and vaginal discharge for two years. Her menses were regular, her last period having begun March 24. Her cervix was large, bilaterally lacerated, eroded, and a thick purulent discharge was in the canal. The fundus was of normal size, retroverted, and a small fibroid was present near the right cornu. On April 6, 1925, curettage, tracheloplasty (Schroeder), left salpingo-oöphorectomy, hysteropexy (Simpson), and appendectomy were performed. Chronic salpingitis was encountered. Histologic examination of the two pieces of cervical tissue removed at operation revealed epidermoid carcinoma. The original specimen, unfortunately, could not be found for re-examination, but the pathologic report, which is quoted herewith, leaves little doubt as to the accuracy of the diagnosis: "Sections of the cervix through the region of the external os show well-preserved stratified squamous epithelium and a few typical cervical glands. In addition round masses of neoplastic epithelial cells are present some distance beneath the surface epithelium. Individual cells show pale staining cytoplasm; the nuclei vary in size and shape and are hyperchromatic. Mitoses are present. Occasionally a small cord of these cells lies free in connective tissue spaces. Lymphocytes surround the tumor. Some of the epithelium is keratinized. The tumor masses invade the cervical glands in some places." On April 16, 1925, 50 mg. of radium was applied in the cervical canal for twenty-four hours; and between April 20 and July 14 the patient received a filtered x-ray treatment through each of six pelvic portals, with the 200 kv. machine at a skin-target distance of 50 cm.—three exposures for thirty minutes each, and three for forty minutes.

Following her discharge from the hospital the patient returned at regular intervals to the Out-Patient Department until 1931. She was not seen again until Nov. 9, 1944, at the age of 53 years. She now stated that during the past

few years, since 1936, she had experienced a foul, blood-tinged vaginal discharge, although she had not menstruated since her previous radiotherapy. Pelvic examination disclosed a hard, friable tumor mass which involved the cervix and adjacent vaginal walls with slight fixation of the parametria. Biopsy of the cervical tumor showed epidermoid carcinoma, grade III. The surface epithelium was ulcerated by a neoplastic growth composed of squamous epithelium with limited keratinization. The cells were loosely arranged, had large nuclei, and numerous mitoses (Fig. 3). The patient's serologic tests for syphilis were positive. During the next few weeks she received twenty deep x-ray treatments through four pelvic portals, a total dose of 6000 r. Several episodes of vaginal bleeding occurred in the course of this treatment, each being managed with vaginal packing and blood transfusion. She received antisyphilitic therapy with bismuth at the same time. The patient was readmitted on Feb. 12, 1945, because of abdominal cramps, weight loss, uremia, and anemia. The tumor had extended to the bladder and rectum with the formation of a vesicovaginal fistula and a rectovaginal fistula. Cystoscopic examination indicated blockage of the right ureter by the tumor. The patient died on May 16, 1945.

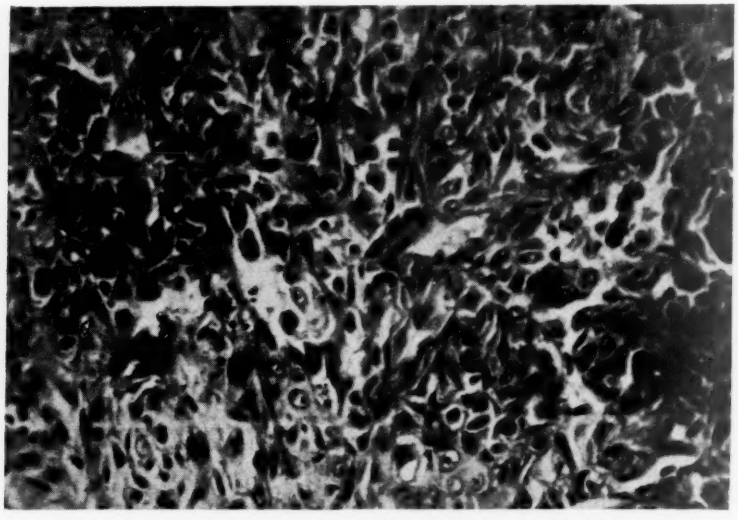


Fig. 3.—Case 2. Cervical biopsy specimen, showing epidermoid carcinoma, nineteen and one-half years after treatment.

Comment

It is impossible to prove that the secondary cervical tumors in these two cases represent recurrences rather than independent cancers. The fact that the histologic types of the secondary tumors correspond with those of the original biopsy specimens makes the presumption reasonable, however, that we are dealing with long delayed recurrences of previously treated cervical cancers. This presumption is strengthened in Case 1, because of the anaplastic nature of the tumor. Since this is the least common of the epidermoid cervical cancer types the chances of an independent new growth of the same type are small. Covington (1947), in reporting recently a similar case of recurrent carcinoma of the cervix seventeen and one-half years after radiation therapy, said that he had never seen a new cancer develop in a cervix which had been treated previ-

ously by radium. These two cases, therefore, are submitted as recurrent cervical cancers which appeared seventeen and one-half years and nineteen and one-half years after initial treatment, respectively. Covington's case and the present two represent the latest local recurrences of epidermoid carcinoma of the cervix of which I have been able to find record.

From a practical clinical standpoint it would seem safe to consider as probably cured any patient with cervical cancer who survives the standard five-year period without evidence of recurrence. Records of the Roosevelt Hospital contain 105 cases, exclusive of the 2 above, in which the time of recurrence could be determined in patients treated with radium. The time intervals are shown in Table I. The average time of recurrence was 14.5 months. Fifty-seven per cent of the recurrences were detected within a year of treatment, and only one recurrence was observed after five years.

TABLE I. INTERVAL BETWEEN TREATMENT AND RECURRENCE IN 105 CASES OF RECURRENT CERVICAL CARCINOMA

INTERVAL (MONTHS)	NUMBER	PER CENT
0- 6	37	35
7-12	23	22
13-24	28	27
25-36	8	8
37-48	7	7
49-60	1	1
over 60	1	1

Summary

The average interval between treatment and recurrence in 105 patients with recurrent epidermoid carcinoma of the cervix treated with radium was 14.5 months. Fifty-seven per cent of the patients manifested their tumor recurrence within a year. Only one recurrence was observed after five years. Two additional cases are reported in which local recurrence of previously irradiated cervical cancer occurred seventeen and one-half years and nineteen and one-half years later, respectively.

Addendum: The present data are at variance with a recent report by D. G. Morton (Am. J. Roentgen. **57:** 685, 1947). Of 45 patients with cervical cancer who survived five years after irradiation therapy, 13 (29 per cent) subsequently died of cancer.

References

Covington, E. E.: J. A. M. A. **133:** 935-936, 1947.
Smith, G. V. S., and Pemberton, F. A.: Surg., Gynec. & Obst. **59:** 1-8, 1934.
Stevenson, C. S., and Scipiades, E.: Surg., Gynec. & Obst. **66:** 822-835, 1938.
Taylor, H. C., Jr., and Guyer, H. B.: AM. J. OBST. & GYNEC. **52:** 451-455, 1946.
TeLinde, R. W., and Galvin, G.: AM. J. OBST. & GYNEC. **48:** 774-794, 1944.

Special Article

PELVIC CANCER DELAY*

The Organization and Observations of the Philadelphia Committee for the Study of Pelvic Cancer

JOHN Y. HOWSON, M.D., PHILADELPHIA, PA.

THE high death rate from cancer today emphasizes the ignorance of its cause, the limitations of present forms of therapy, and the failure to diagnose it while still favorable for treatment. What measure of success we enjoy is limited to that small group of fortunate patients in whom an early diagnosis is achieved. A greater effort must be made to prevent its development and to find it at its inception.

The problems of making an early diagnosis of cancer have long been recognized. For instance, the very location of a malignant growth often precludes our ability to find it. In contrast, accessible lesions afford no reasonable excuse for delay in their early discovery. Most malignancies occurring in the female pelvis fall into this latter category. Basically, therefore, the early discovery of cancer so located is dependent on the prompt action of the patient at the first sign of trouble; and likewise on the physician's immediate discharge of his duty at her first visit.

It has been shown frequently that the physician is an important factor contributing to delay in the early diagnosis of cancer. The very life and death of an individual may depend on the physician's degree of suspicion of cancer, his ability to recognize its early stages, and upon his ultimate recommendation. If, as it seems, the physician is a contributor to delay in the diagnosis of early cancer, then something beyond mere criticism is indicated. Remedial suggestions have been made many times, but no practical educational program for the general practitioner or physicians in general has ever been established.

Two years ago a group of physicians in Philadelphia proposed a plan whereby they hoped to stimulate physicians to recognize their responsibility in regards to the diagnostic delay period in patients suffering with pelvic cancer. In brief it was proposed:

1. To form a committee of gynecologists who would study all pelvic cancer cases in Philadelphia with special reference to the sequence of events occurring between the onset of the patient's first symptoms, a definite diagnosis and adequate treatment.

2. To utilize the facts obtained from this study to inform the medical profession of their importance in diminishing the delay in diagnosis of pelvic cancer.

*Read before the Philadelphia Obstetrical Society, Feb. 6, 1947.

The project was accepted and sponsored by the Philadelphia Obstetrical Society. Such a committee was appointed and received the approval of both the Philadelphia Department of Public Health and the Philadelphia County Medical Society. Headquarters were established in the County Medical Society Building and the American Cancer Society granted funds, sufficient to permit the employment of a full-time investigator to carry out the actual work.

The principal hospitals of Philadelphia soon gave their full cooperation to this undertaking. They granted permission for the Committee's investigator to enter their wards and out-patient clinics for direct questioning of each patient suffering with pelvic cancer. At the present time the Committee has access to such patients in 19 different institutions, which include all of the teaching hospitals. A questionnaire designed for its brevity, clarity, and chronological disclosure of facts about the delay period has been used to help correlate and record the desired information.

Method of Utilization of Material

The Committee meets monthly. Prior to each meeting the cases investigated during the preceding month are classified into two main groups: those cases revealing no delay and those cases with an apparent delay. The cases with an apparent delay are then subdivided into three categories: (1) delay due to the patient, (2) delay due to the physician, and (3) delay due to both the patient and the physician. The cases showing physician delay are further scrutinized for detailed discussion at the time of the next meeting.

In March, 1946, the custom was instituted of inviting any physician intimately connected with the cases exhibiting delay to meet with the Committee to participate in the discussion. This was necessary for two reasons: The information obtained by our questionnaire was entirely that voiced by the patient. Knowing the frequent inaccuracy of patients' statements the Committee felt that in no case should the responsibility for delay be ascribed to a physician without affording him the opportunity to present the facts as he knew them. The second reason for inviting the family physician, and the main one, was to begin a program of education among the physicians of this city. Specifically the group wished to create a higher index of suspicion for pelvic cancer, emphasizing the importance of making adequate pelvic examinations and early diagnoses. The Committee was anxious to reveal the true causes of physician delay as they were brought to light by the survey and to take active steps to correct them.

Getting the busy doctor to attend the meetings at first posed a problem, since no physician is anxious to be censored or questioned as to his efficiency in the handling of his patients. In order to reach the physicians in question, a letter was written to each one, inviting him to attend the meetings to further disclose the details of the case history as he knew it. It was explained that the purpose of the Committee was not to ridicule or castigate anyone, but it was necessary to obtain all the facts before determining the existence of a true delay or what could be done to prevent a similar delay in the future. To date twenty-seven physicians have met with this Committee. The response and cooperation of these physicians have been most encouraging.

The meetings have been informal and friendly, yet the discussions have been serious and stimulating. The physicians who have met with the Committee have been dealt with in a friendly way and there has been a mutual exchange of ideas between the general practitioners and the specialists in Gynecology. When a

delay by the physician is disclosed, little emphasis and importance are placed on this in itself. The underlying reason for the delay is the important topic of discussion. For example, when the delay resulted from failure to take a biopsy, the discussion will evolve around the question of whether a general practitioner should attempt cervical biopsy. If so, what equipment should he have available? Should he biopsy all cervices showing erosion? How should he decide the need of a biopsy? At the conclusion of the discussion, the helpful suggestions and the constructive criticism have been a lesson to all present. The physician who failed to take the biopsy has been forgotten, and this is as it should be.

Summary of Results

Between Nov. 1, 1945, and Jan. 1, 1947, some 455 living patients with pelvic cancer were investigated. Of this number, in 145, or 31.8 per cent, there had been no delay. The remaining 310, or 68.1 per cent of the cases, demonstrated a lapse of one or more months from the time the symptoms were first noted until a correct diagnosis was made and adequate treatment instituted.

Number of cases investigated			455
No delay	145	31.8%	
Delay of more than one month	310	68.1%	

Of these 310 cases showing a delay it was found that the patient alone was responsible in 197, or 63.6 per cent; the physician alone was at fault in 76, or 24.5 per cent, of the cases. In 37, or 12.0 per cent, of the cases, the patient and the physician were equally dilatory. Thus the combined total involving the physician was 113 cases, or 36.5 per cent.

Number of cases showing delay			310
Responsibility—			
Patient	197	63.6%	
Physician	76	24.5%	
Physician and patient	37	12.0%	

In 93, or 82.3 per cent, of the cases, one physician contributed to the delay. In 17, or 15.0 per cent, of the cases, two physicians were involved in the delay of each patient. Three physicians were dilatory in three of the cases, or 2.6 per cent. It should be noted that in the 113 cases showing physician delay there was a total of 136 doctors responsible—which truly is a more revealing index of the problem at hand.

Number of cases showing physician delay			113
Delay by one physician	93	82.3%	
Delay by two physicians	17	15.0%	
Delay by three physicians	3	2.6%	
136 physicians involved in 113 cases			

These figures demonstrate that the physician plays an active part in the problem of a delay in early diagnosis. Thus in a small way a program has been launched for educating the physician (be he specialist or general practitioner) to the opportunity afforded him to make an early diagnosis in cases of pelvic cancer. The Committee believes that such a program can become an influential contribution for obtaining earlier diagnoses in pelvic cancer and thus a better salvage of patients afflicted with this disease.

Editorial

ECLAMPSIA

Several reports on the etiology of eclampsia are based on the premise that the disease is primarily a hypertension due to spasm of the arterioles. Most investigators, however, believe that eclampsia—pre-eclampsia is a clinical entity in which there is first a water and salt retention due to an abnormal capillary permeability. Some of the patients develop hypertension (which may be compensatory), proteinuria, and a very few have various other symptoms and signs due to cerebral anemia, culminating in convulsions and coma.

Grollman stated that if the Goldblatt clamp is properly placed on the renal artery there is no increase in the blood pressure during pregnancy, or if there is a hypertension before pregnancy, that the blood pressure decreases to normal. The acute toxemia described by some investigators as a result of constricting the renal artery is due to too great a constriction. He thinks that the normal blood pressure is due to the increased vascular bed resulting from the pregnancy.

Smith and Smith still believe that a deficiency of estrogen and progesterone, as well as abnormal oxidation of the estrogens is associated with certain pathologic changes in the placental syncytium resulting in a failure of the latter to utilize chorionic gonadotropin. The result of this abnormal hormone and placental metabolism is the production of a protein similar to menstrual toxin. This toxin according to them is the cause of pre-eclampsia. They have treated a small group of patients with a protective pseudoglobulin which they think has resulted in clinical improvement. It is difficult for one to see any striking effects of this neutralizing protein fraction.

Grollman states that hyperfunction of the posterior lobe or the basophilic cells has no connection with the etiology of eclampsia or hypertension. He also states that it remains to be proved that hormonal aberration is the cause of toxemia and not the result of some fundamental process.

Several investigators have reported the production of the periportal hemorrhage and necrosis in experimental animals by various procedures. Dieckmann has observed several patients who showed no evidence of eclampsia prior to death, yet the liver showed the typical lesion of eclampsia. He believes that the periportal hemorrhages found in the liver are peculiar to the pregnant woman under certain conditions, but are not pathognomonic of eclampsia. A recent report indicates that thickening of the basement membrane is not always present in eclamptic patients. Thus there is no pathologic lesion either in the liver or the kidney characteristic of eclampsia.

Since the liver and kidney lesions are not peculiar to eclampsia—pre-eclampsia, and, since the Goldblatt kidney does not produce eclampsia, it seems that animal experimentation is of little value in determining the etiology of eclampsia.

Several reports indicate that there is no abnormal renal physiology in eclampsia—pre-eclampsia. This is difficult to believe, especially since all the studies were made when the patients were secreting urine and not during the anuric phase of the disease.

One investigator states that repeated injections of Veratrone (veratrum virides) does cause a reduction in blood pressure, but at the same time there is a marked reduction in urinary output. He concludes that the use of Veratrone is contraindicated in the treatment of pre-eclampsia—eclampsia.

Several reports have been published claiming that the injection of plasma has been of great benefit in the treatment of eclampsia. Eclampsia is such a protean disease, being readily curable if early delivery occurs, that it requires a large number of cases to properly evaluate a specific treatment.

Reports are still being published in which eclampsia is attributed to faulty diet. This seems difficult to prove and certainly in most clinics eclampsia is rare, but pre-eclampsia still occurs even in patients who have been on a reasonably adequate diet.

High spinal anesthesia, especially with the catheter technique, seems of proved value in the treatment of the cardiac failure with pulmonary edema that is such a serious complication of eclampsia. If this work is confirmed, it is the most important contribution to the treatment of eclampsia—pre-eclampsia that has been developed in the past decade.

Since eclampsia—pre-eclampsia is an entity peculiar to the human race, studies as to the etiology and treatment must be made on pregnant patients and not on animals.

W. J. D.

Necrology

FRANK FARROW SIMPSON, long associated as gynecologist with the hospitals of Pittsburgh, Pennsylvania, died on Feb. 10, 1948, in Honolulu, T.H., where he resided since his retirement about twenty years ago. He was born in 1868, graduated with a baccalaureate degree from the University of South Carolina in 1889, and received his M.D. at the University of Pennsylvania in 1893. He was President of the American Gynecological Society in 1917, Vice-President of the American Association of Obstetricians and Gynecologists in 1905, Secretary General of the Seventh International Congress for Obstetricians and Gynecologists in 1912, section chairman of the American Medical Association, in 1912, Chief of the Medical Section, Council of National Defense, 1917-1918, and Lieutenant-Colonel Medical Corps, United States Army.

Department of Reviews and Abstracts

Selected Abstracts

Malignancies

Cantone, C.: Carcinoma of the Stump After Supravaginal Hysterectomy, La Ginecologia **12:** 285, 1946.

During the period between 1938 and 1944, carcinoma of the stump after supravaginal hysterectomy was observed in the Department of Obstetrics and Gynecology of Vercelli in 0.67 per cent of the cases.

Mortality rate, after total hysterectomies (excluding operations performed for carcinoma), reached 2.50 per cent, while in cases of supravaginals the mortality was reduced to 1.38 per cent. The number of total hysterectomies during the above-mentioned years was 182, the number of subtotal hysterectomies 595.

Cantone recalls the opinion of some gynecologists in this country, that in hospitals where hysterectomies are not very frequently performed, the supravaginal operation should be considered the method of choice, if a definite indication for a total hysterectomy is not present, but believes that the matter requires further investigation. GEMMA BARZILAI.

Furth, J., and Sobel, H.: Hypervolemia Secondary to Grafted Granulosa-Cell Tumor, J. Nat. Cancer Inst. **7:** 103, 1946.

Hypervolemia (increased blood volume) occurs in mice engrafted with certain, but not all, strains of granulosa cell tumor. It amounts to over twice the average volume found in normal animals, or in mice bearing other tumors. There is an increase in plasma volume (in contrast with human polycythemia), a twofold increase in total red cells, and in cells per unit weight; and a slight fall in red-cell count and in hematocrit. At necropsy there is marked congestion of liver, spleen, adrenals, and bone-marrow. The hypervolemia does not parallel the tumor size, the amount of organ congestion, nor the extent of estrogenic change. It does not follow massive doses of estrogens alone.

These tumors evidently produce a substance which affects the blood volume mechanism, and cause the appearance of blood changes like those seen in pregnancy. The substance may be a hormone like those secreted by the adrenal cortex. IRVING L. FRANK.

Endocrinology

Baidins, Von A., Claesson, L., and Westman, A.: On the Influence of Roentgen Treatment Upon the Gonadotrophic Function of the Pituitary, Gynaecologia **122:** 347-362, 1946.

The authors, reporting from the Woman's Clinic of Karolinska, Stockholm, attempted to re-evaluate the gonadotrophic function of the pituitary gland after x-ray treatment. In their opinions this problem was unsolved. The authors, therefore, investigated the influence of x-rays upon the gonadotrophic function of immature female white rats, using 61 animals of which 38 were in their study groups and 23 were employed as controls.

The essayists concluded that it was impossible to influence the pituitary gland of 27 white female infantile rats with small doses of x-ray, 2 to 45 roentgen units; and, in such cases, the ovaries could not be stimulated. The anatomic findings confirmed the biological studies. Dissection and histologic investigations did not show any special difference between the experimental and 12 control animals. Increased function of the pituitary could not be observed biologically or by morphologic changes.

The eight rats treated with 50 to 1,000 roentgen units, or their eight controls, did not reveal any irregularities of ovarian function nor histologic changes of ovaries or pituitary glands. C. E. FOLSOME.

Gynecology

Matus, V., and Moreno, G. M.: Importance of Puncture of Cul-de-Sac of Douglas in Gynecology, Bol. Soc. chilena de obst. y ginec. 11: 23-27, 1946.

During the years 1944-45, pelvic puncture was employed 111 times. The indications were as follows: tubal pregnancy, 50; pelvic abscess, 35; postoperative complications, 8; peritonitis, 6; no diagnosis (blank puncture), 5; tuboovarian abscess, 4; infected hematocele, 1; ovarian cyst, 1; and ruptured bladder, 1.

The authors believe that pelvic puncture is a very helpful procedure. They compare its usefulness with three other procedures used in gynecology, namely, the Schilling hemogram, endometrial biopsy, and the Friedman pregnancy test. J. P. GREENHILL.

de Moraes, A., and do Amaral, C.: Concerning Cases of Tuberculosis of the Female Genitalia, An. brasil de ginec. 22: 255-262, 1946.

During the last two years, the authors observed eight cases of tuberculosis of the female genitalia among 954 patients operated on at the Gynecological Clinic of the National Faculty of Medicine of the University of Brazil. This represents an incidence of 0.84 per cent. The authors discuss the diagnosis of this condition and they particularly emphasize the importance of making microscopic examinations of all tissue removed at operation.

Gynecologic Operations

Brindeau, A., Lantuejoul, P., and Hubert, L.: The Use of Ovular Membranes in Creation of an Artificial Vagina, Gynec. et obst. 45: 417, 1946.

A third successful creation of an artificial vagina, by a technique published by Brindeau in 1938, is recounted. With a sound in the bladder, and a guiding finger in the rectum, a channel is created through the perineum, between whatever labial structures are present. This channel is then lined with ovular membranes obtained at a simultaneous cesarean section. The membrane sac is anchored to the vault with a few sutures, and the free edges are united with the margins of the original U-shaped perineal skin incision. The lined canal thus produced is packed for a week with gauze soaked with horse serum, and for a second week with gauze soaked in cod liver oil. Thereafter the patient inserts a No. 20 Hegar bougie daily for six weeks to prevent stenosis during the healing process. The membranes are gradually replaced by epithelium, and the patient reported had a good functional result. The authors have done preliminary laparotomies in these cases. IRVING L. FRANK.

Judd, George E.: Preservation of the Upper Pelvic Floor and Bladder Support in Total Hysterectomy, West. J. Surg. 55: 209, 1947.

A historical review of total hysterectomy is presented. The chief support of the uterus is the endopelvic fascia which covers the pelvic organs below the visceral peritoneum. In some cases the fascia is strengthened and forms true ligaments notably in the base of the broad ligaments; posteriorly it forms the uterosacral ligaments and anteriorly the uteropubic ligaments. Cystocele is primarily a hernia of the bladder through a break in the uteropubic fascia. Prolapse of the uterus results from laceration or stretching of the endopelvic fascia, laterally and posteriorly.

The author describes and illustrates his technique for total hysterectomy based on the above anatomic knowledge. The broad ligaments are cut and ligated, and the uterine vessels ligated and cut. A cuff of the endopelvic fascia is then made by a circular incision around the cervix. The anterior cuff is pushed down along with the bladder; the posterior is pushed along with the uterosacral ligaments, and the lateral or cardinal ligaments are dissected free of the uterus and ligated. The vagina is entered posteriorly, and a circular incision made to remove the uterus. Sulfanilamide powder is put in the vagina. The vaginal cuff is closed and then the fascial cuff, including the cardinal ligaments laterally and the uterosacral ligaments posteriorly, is sutured over the vaginal vault. Where a cystocele exists the uteropubic fascia is approximated to provide a new floor for the bladder. The entire area is peritonealized by suturing over with the peritoneal fold of the bladder. WILLIAM BICKERS.

Menopause

Taylor, R. D., Corcoran, A. C., and Page, Irvine H.: Menopausal Hypertension: A Critical Study, Am. J. M. Sc. 213: 475-476, 1947.

The authors, reporting from the Lilley Laboratory for Clinical Research, Indianapolis City Hospital, followed 179 castrated women and twenty-one with the natural menopause. They demonstrated, in these cases, that arterial hypertension was no more common in them than in the general population. "Vasomotor instability," as exhibited by "hot flashes," perspiration, and tachycardia were not necessarily associated with hypertension, and their alleviation by estrogens need not affect arterial pressure.

The menopause seemed to intensify pre-existing psychonouroses. Despite severe neurotic behavior, hypertension did not develop within three or more years except in six of those 200 subjects. From these data the authors conclude that the relationship of the menopause and hypertension was incidental, and the loss of ovarian secretion was neither a primary nor a contributory cause of arterial hypertension. C. E. FOLSOME.

Newborn

Rossi, Antonio: Weight and Length of Newborn, Ginecologia 12: 100, 1946.

Rossi reviews weight and length of newborn babies, and the weight of the placenta, of confinement cases in Novara, Italy, from 1937 to 1943. A definite decrease in weight, length of the babies, as well as a reduction in the weight of the placenta is noted. This applies to the population as a whole, as well as to different social and financial groups: housewives, factory workers, women from rural districts.

The average weight of the newborn babies for the entire population in 1937 amounted to 3,236 Gm., and in 1943 it decreased to 3,030.8 Gm. The average length of the newborn was 50 cm. in 1937, and decreased to 49.5 in 1943. The weight of the placenta was 547 Gm. in 1937, and 526 Gm. in 1943. On considering weight differences in the various social groups, one finds in the group of babies of housewives a decrease from 3,330.9 Gm. to 3,063.5 Gm. in weight; 50.3 cm. in 1937 to 49.7 cm. in 1943 in length; and a decrease in placenta weight from 552 Gm. to 521 Gm. In the factory workers, the most underprivileged group in Italy, the weight of the newborn babies reached a low of 2,955.6 Gm. in 1943, as compared with 3,142.5 Gm. in 1937. The length of the babies showed a decrease from 49.6 cm. to 49.2 cm., and the weight of the placenta was reduced to 517 Gm., as compared with the average weight of 541 Gm. in 1937. In the rural districts, the decrease was less spectacular. From an average weight of 3,197 Gm. in 1937, there was a drop to an average of 3,077 Gm. in 1943. From a length of 50 cm., there was a decrease to 49.6 cm., and the weight of the placenta decreased to 528 Gm. from the average 538 Gm. in 1937.

Conclusion: A definite reduction of the length and weight of the fetus, and of the weight of the placenta, which—although showing some differences in favor of the babies of women in rural districts, and a maximum drop in the group of factory workers—is equally noted in the population as a whole, and must therefore be credited to the deterioration of nutrition and emotional strains associated with war. GEMMA BARZILAI.

Mustakallio, M. J.: On Congenital Sincipital Encephalocele and Its Treatment, With Special Reference to the Structure of the Wall, Ann. Chirurg. et Gynec. Fenniae 35: Supplement 2, 1946.

A monograph on the subject of congenital encephaloceles is presented. The literature on the subject, going back as far as the early part of the eighteenth century is covered in detail. Four cases of sincipital encephalocele, all of which were operated and all of which recovered, are then reported. Two were female infants; one three weeks old, and the other seven months old. The other two were a male of 17 years and a female 20 years of age. The symptoms, differential diagnosis, prognosis, and treatment of the condition are then discussed. It is stated that Dandy felt that operation should be postponed until the infant was one year old. However, the results shown by the author in the two infants operated would tend to contradict this.

A detailed study was made of the tissue removed from three of the four cases and anyone interested in this subject would be well advised to refer to this section of the monograph. Finally, in discussing the etiology the author states that, inasmuch as there have been several reports of two or even three cases in the same family, "we must assume that some endogenic factor does exist." HERBERT J. SIMON.

Nelson, T. Y.: Intracranial Damage in the Newly Born, M. J. Australia 1: 268, 1947.

The author wishes to stress the group of cases in which the intracranial damage is so great and the symptoms are so severe that the question of survival is in doubt. The subdural type of hemorrhage is the most frequent and the intracerebral the most infrequent. The various signs and symptoms referable to the different types of intracranial hemorrhage are described. A detailed description of subdural hemorrhage is given as well as means of substantiating this diagnosis.

Early diagnosis and appropriate treatment are essential if the baby is to survive. The author feels that if the presence of blood in the subdural space can be established, the blood should be evacuated as early and as completely as possible. WILLIAM BERMAN.

Maternal Vitamin A Intake and Ocular Abnormalities in the Offspring,* Nutrition Rev. 5: 89, 1947.

The eyes of young, born of rats markedly deficient in vitamin A, show a variety of major anatomic defects and distortions. For these to appear, the maternal serum vitamin A must be one-tenth normal or less; a level at which 25 per cent of the mothers die, fetal resorption is common, and normal birth impossible. At slightly higher levels the eyes show no change whatever. Therefore, it is reasoned that congenital retrolental fibroplasia, which occurs in 8 per cent of infants weighing less than 5 pounds at birth, is probably unrelated to vitamin A deficiency. IRVING L. FRANK.

Fukas, Von M.: Streptococcic Sepsis of the Newborn From Mastitis in the Pregnant Mother, Gynaecologia 123: 53-57, 1947.

Fukas, of Athens, reports an unusual case where a normal male infant was delivered without maternal complications. The baby was apparently in excellent health until three days of age, and ultimately died of streptococcal septicemia. Autopsy confirmed the diagnosis. The mother had suffered from serious mastitis of the left breast for two months prior to delivery. The author was of the opinion that the portal of entrance to the baby was via hematogenous transmission of streptococci in utero, and that the spread of infection occurred in the baby when the antibodies from the mother had been overcome by the overwhelming infection. The placenta was negative to histologic study. C. E. FOLSOME.

*This is a review article, based on papers of:
1. Warnaky, J., and Schraffenberger, E.: Proc. Soc. Exper. Biol. & Med. 57: 49, 1944.
2. Jackson, B., and Kinsey, V. E.: Am. J. Ophth. 29: 1234, 1946.

Pregnancy

Belvederi and Morano: Ophthalmoscopy Study of the Eyeground in Pregnancy, Riv. ital. di ginec. **28:** 3, 1945.

Belvederi and Morano of the Medical School of Bologna studied retina changes in 142 cases of normal and impaired pregnancies. They found venous hyperemia, retinal vessel spasm, retinal edema, and cottonwool exudate, hemorrhages, macular stars, detachment of the retina, and amaurosis.

They discuss the relationship of those ocular signs and symptoms to findings in cases of pregnancy showing no other pathologic change, in cases associated with renal diseases, or associated with toxic changes.

In cases of otherwise normal pregnancy, venous hyperemia was present in 36 per cent, retinal spasm in 38 per cent, edema in 30 per cent, and retinal stars in 4 per cent of the cases.

In pre-eclampsia, 22 per cent of the cases showed normal eyegrounds; 44 per cent showed venous hyperemia; 38 per cent, retinal spasm; 51 per cent, retinal edema; 15 per cent, retinal stars; 9 per cent hemorrhages; 2 per cent, detachment of the retina.

In cases of renal disease in pregnancy, the eyeground was normal in 37 per cent, there was venous hyperemia in 62 per cent of the cases. Retinal arterial spasm was present in 25 per cent of the cases, retinal edema in 50 per cent, retinal stars in 37 per cent, retinal hemorrhages in 12 per cent.

In cases with severe eclampsia, the eyeground was normal only in 15 per cent of the cases, venous hyperemia was present in 47 per cent, arterial spasm in 43 per cent, retinal edema in 75 per cent, outlined macular stars in 43 per cent, retinal hemorrhages in 34 per cent, detachment of the retina in 6 per cent, amaurosis in 9 per cent of the cases.

On the basis of their findings, the authors advocate routine eyeground examinations on all pregnant women, and repeated examinations in all cases associated with more or less obvious symptoms of toxic changes, or of renal diseases. GEMMA BARZILAI.

Gianaroli, L.: Capillary Fragility in Pregnancy, Riv. ital. di ginec. **28:** 225, 1945.

Studies conducted during wartime by Gianaroli on women at various stages of gestation indicate that a latent vitamin C deficiency was present throughout among pregnant women in the obstetric department of the Medical School in Bologna.

Vitamin C deficiency was evaluated indirectly by approaching capillary fragility. This was done by Cianci's method, that consists in counting the petechiae appearing at bend of elbow, following the application of a suction bell.

During pregnancy and during puerperium, abnormal capillary fragility was demonstrated. It was, however, readily lowered by oral supply of 200 mg. vitamin C daily for seven consecutive days, while a much higher dose was requested to reduce capillary fragility during the puerperium. This shows that in the puerperium there was a higher degree of vitamin C reserve deficiency.

The result of this evaluation of latent vitamin C deficiency through demonstration of capillary fragility parallels findings by Maciotta in earlier research in the same medical school in which vitamin C content of blood and urine was measured in different stages of gestation. GEMMA BARZILAI.

Toxemia

Umberto, Bracale: Blood and Bone Marrow Disorders Associated With Eclampsia, Arch. di obstet. e ginec. **51:** 245, 1947.

In a series of 21 pregnant women, with eclampsia, blood and bone marrow elements were studied. In the peripheric blood, erythrocytes, hemoglobin, and lymphocytes appeared reduced in number, while leucocytes were numerically increased.

In the bone marrow that was obtained by puncture of the sternum, anisocytosis, microcytosis, and macrocytosis were present in the elements of the red series. Hemohistioblasts were increased, and the red and white cell index shifted toward the latter. Myelocytes were definitely increased. As a whole the blood picture revealed alterations in both red and white elements. GEMMA BARZILAI.

Correspondence

Induction of Labor

To the Editor:

I have read with great interest the report of the discussion on the induction of labor which took place at the Chicago Gynecological Society in November, 1946, and was published in the JOURNAL in September, 1947 (p. 496).

Most British obstetricians will agree with the general conclusions therein, but there is one comment I should like to make on the methods advocated for inducing premature labor.

As Dieckmann and McCready state in their article, the Drew-Smythe catheter is used extensively in British hospitals, and indeed it is the almost universal method of choice. Bags, bougies, etc., are now rarely used, and many of us in this country have long been surprised at the retention of these cumbersome and dangerous instruments by American obstetricians. The reluctance to adopt the catheter method is also curiously conservative. This method carries the great advantage of leaving the forewaters, and consequently the uterine bacteriologic barrier, intact, and has drastically reduced the incidence of infection. As Dieckmann says, labor does not ensue immediately in all, but it does in the great majority of cases, and in any event the procedure may be repeated twice, or even three times.

Simultaneous stimulation with a complete medical induction is a useful reinforcement, and the danger of hemorrhage from damage to the placenta is negligible in careful hands.

ALBERT DAVIS.

93 HARLEY STREET,
LONDON, DEC. 31, 1947.

Drainage of a Hydrocephalic Head

To the Editor:

D. N. Danforth (AM. J. OBST. & GYNEC. 54: 694-695, 1947) presents a modification of the procedure mentioned by Stander for decompressing and draining a hydrocephalic head in a breech presentation. Still another slight modification, available when the spinal canal is opened in the cervical region, consists in using a metallic catheter for passage into the distended ventricles. This variation permits easy collection of the fluids, so that it may be measured for the record.

When there is a spina bifida, as so often happens, a metallic or stiff silk catheter, depending upon the location of the defect, may be passed through the defect in the vertebral arches. Moreover, when the hydrocephalic head presents by the vertex, its fluid contents may be easily drained through a regular abdominal paracentesis trocar passed through an open suture under sight or touch.

These procedures have been employed for many years and have greatly simplified the management of labor complicated by cephalopelvic disproportion on the basis of hydrocephalus, but are rarely mentioned in standard textbooks. They are so much simpler than the classic technics that their general adoption would seem indicated.

E. D. PLASS, M.D.

IOWA CITY, IOWA
Nov. 3, 1947

Screw Type Cervical Cannula

To the Editor:

I have read, with much interest, the letter of Dr. Paul Titus which appeared in your June (1947) issue; also, the discussion in the November issue.

As one who, for a number of years, has been especially interested in the screw-thread-tip cannula, I was greatly interested in Dr. Titus' remarks, advising against its use.

I should like, very much, to know whether this opinion is based upon theoretical considerations—or whether Dr. Titus has actually had unfavorable experiences with this type of cannula.

I ask this question because I have used this type of cannula over a period of many years and have followed through the results—not only following the examination but also after delivery; this observation covering a number of years. To date, I have not found any unfavorable results from the use of this instrument. Neither have I had one report of any specific case of injury or disturbance following its use.

If, however, definite cases of injury have been observed, they should be specifically and scientifically reported. It is for this reason that I ask the definite question.

I receive frequent requests for information concerning this technique, and I should like to be specific and accurate in my replies.

The observations and experiences of Dr. Titus—and of others who have used this technique—would be greatly appreciated.

A. P. Hudgins, M.D.

Charleston, W. Va.
Dec. 6, 1947

Hysterosalpingography—Reply by Dr. Bickers

To the Editor:

The discussion relative to the various procedures in current use relative to "Hysterosalpingography" which appeared in the February, June, and November, 1947, issues of your journal has aroused my interest. Specifically I am concerned over the reference of Dr. Titus and Dr. Weisman to the trauma which they have observed incident to the use of the screw type cannula. This instrument, which was introduced several years ago by Dr. A. P. Hudgins, has so greatly facilitated and expedited hysterosalpingography as an office procedure that I am among those who feel that the instrument has real merit, and its place in the study of human sterility is an important one.

The screw type cervical cannula has been used by me for 112 hysterosalpingographys on 104 patients. In each case the cannula was removed immediately after the x-ray study was completed, and in no case was there any bleeding following the removal. This would seem to indicate that there was little trauma associated with its use. Indeed, it is my impression that this instrument produces less trauma than the tenaculum which is necessary when one uses the conventional type of cannula. In checking the records on these patients hurriedly I have not been impressed with any increased incidence of cervical erosion nor chronic endocervicitis following the use of this cannula. The ease with which it can be used, the minimum discomfort to the patient, the vastly improved uterine filling and the complete absence of any evidence of trauma to the cervix would seem to permit unqualified recommendation of its use.

William Bickers, M.D.

Richmond, Va.
Dec. 28, 1947

Items

American Board of Obstetrics and Gynecology, Inc.

Examinations

The general oral and pathology examinations (Part II) for all candidates will be conducted in Washington, D. C., by the American Board of Obstetrics and Gynecology from Sunday, May 16, through Saturday, May 22, 1948. The Shoreham Hotel in Washington will be the headquarters. Formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Hotel reservations may be made by writing direct to the Shoreham Hotel.

Candidates for re-examination in Part II must make written application to the Secretary's Office not later than April 1, 1948.

Candidates in military service are requested to keep the Secretary's Office informed of any change in address.

Applications are now being and will be received until November 1, 1948, for the 1949 examinations. For further information and application blanks, address Paul Titus, M.D., Secretary, 1015 Highland Building, Pittsburgh 6, Pa.

PAUL TITUS, M.D.
Secretary.

Notice to Diplomates

American Board of Obstetrics and Gynecology, Inc.

The forthcoming fourth edition of the Directory of Medical Specialists plans to designate by appropriate abbreviations whether Diplomates of the above Board practice both branches of the specialty or major in one or the other. The letters OG will be used to indicate combination of practice in both branches, the letter O that the Diplomate majors in obstetrics, and the letter G that he majors in gynecology.

Diplomates who have not already notified the Directory Publication office on this matter in making their biographic returns should communicate with the Directory of Medical Specialists, 210 East Ohio Street, Chicago, Illinois.

PAUL TITUS, M.D.
Secretary.

Erratum

In the article by Lois A. Day, Robert D. Mussey, and Robert W. DeVoe, entitled "The Intrauterine Pack in the Management of Postpartum Hemorrhage," in the February issue of the JOURNAL, on page 234, in the third line above Table II, "276 patients" should read, "267 patients."